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Comprehensive Invited Review

From molecular mechanisms to clinical management of antineoplastic drug-induced cardiovascular toxicity: A translational overview

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Abstract

Significance: Antineoplastic therapies have improved the prognosis of oncology patients significantly.

However, these treatments can bring to a higher incidence of side effects, including the worrying cardiovascular toxicity (CTX).

Recent Advances: Substantial evidence indicates multiple mechanisms of CTX, with redox mechanisms playing a key role. Recent data singled out mitochondria as key targets for antineoplastic drug-induced CTX; understanding the underlying mechanisms is therefore crucial for effective cardioprotection, without compromising the efficacy of anti-cancer treatments.

Critical Issues: CTX can occur within a few days or many years after treatment. Type I CTX is associated with irreversible cardiac cell injury, and is typically caused by anthracyclines and traditional chemotherapeutics. Type II CTX is generally caused by novel biologics and more targeted drugs, and is associated with reversible myocardial dysfunction. Therefore, patients undergoing anti-cancer treatments should be closely monitored, and patients at risk of CTX should be identified before beginning treatment to reduce CTX-related morbidity.

Future Directions: Genetic profiling of clinical risk factors and an integrated approach using molecular, imaging, and clinical data may allow the recognition of patients at high-risk of developing chemotherapy-related CTX, and may suggest methodologies to limit damage in a wider range of patients. The involvement of redox mechanisms in cancer biology and anticancer treatments are a very active field of research. Further investigations will be necessary to uncover the hallmarks of cancer from a redox perspective and to develop more efficacious antineoplastic therapies that also spare the cardiovascular system.

1. Introduction: The clinical problem of antineoplastic drug cardiovascular toxicity

During the last years, the prognosis of cancer has been greatly enhanced by advancements in antitumoral therapeutic protocols; many types of malignancies can now be cured or maintained in remission for a long time, allowing patients to live the rest of their lives in remission from cancer (22, 132, 173, 267, 392). Unfortunately, antitumoral treatments exert some adverse side effects (Table 1). The cardiovascular (CV) system can be negatively affected by such therapies, and this is especially true in the so-called long-term cancer survivors, since the likelihood that cardiac side effects of antitumoral treatments become the main health problem after tumor elimination increases with survival (250, 287, 429, 432). The most common CV complications of antineoplastic therapies include vasospastic and thromboembolic ischemia, arterial hypertension, dysrhythmia, and left ventricular (LV) dysfunction, leading to heart failure (HF) (25, 204, 376, 429, 432). Cardiac dysfunction caused by *anthracyclines* (ANTs) has long been known as the main form of anti-cancer drug-induced cardiotoxicity (CTX) (91-94), with production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) being considered main cytotoxic mechanisms (see Section 10 for details). In the last decades, new biologic anti-cancer drugs, such as intracellular signaling inhibitors, are being increasingly used. These molecules may also be cardiotoxic, since they block pathways that are major modulators of myocardial function, especially under conditions of cardiac stress, such as hypertension or hypertrophy (376), with mechanisms of action that often involve redox signaling, too. As an example, drugs that target the human epidermal growth factor receptor 2 (*HER/ErbB2*) and the vascular endothelial growth factor (*VEGF*), exert a considerable adverse effect on myocardial function via different mechanisms, based on the role of the proteins inhibited. The toxicity produced by biologic drugs seems to be due to mechanisms other than cardiomyocyte disruption, is most often reversible with discontinuation of the drugs, and has been classified as type II CTX (93, 94). On the other hand, ANTs produce a form of cardiac dysfunction which is typically irreversible, termed type I CTX, and which is characterized by evident ultrastructural myocardial abnormalities (93, 94). Of note, these two CTX paradigms may overlap. One paradigmatic example is the

ErbB2 receptor inhibitor *trastuzumab*, that can cause irreversible LV dysfunction in patients previously treated with ANTs (376, 432), with the neuregulin/ErbB2 pathway which seems to modulate the increase in ROS caused ANTs (390).

In this manuscript, we address the main cellular and molecular mechanisms and pathophysiologic and clinical characteristics of antineoplastic drug-related CTX, since only a comprehensive assessment of this phenomenon can provide important hints to predict, treat, and prevent it. Special emphasis is placed on LV dysfunction and HF, in consideration of their clinical and social burden (25, 125), with updated insights concerning the role of oxidative damage, a mechanism that appears to have a major role in antineoplastic drug-induced CTX (412, 432). Whenever appropriate, we divided the various Sections in three categories a) adverse effects, b) mechanisms of adverse effects and c) ways to reduce cardiovascular toxicity.

2. Anthracyclines (ANTs)

Among the drugs with greater cardiotoxic potential, ANTs are good representatives of the type I CTX paradigm. ANTs are widely used and effective antineoplastic drugs, indicated for the therapy of many kinds of cancers including lymphomas, leukemias, and sarcomas, and for both early and advanced breast cancer. However, these drugs have been recognized as cardiotoxic since the 1960s (384). *Adverse effects:* ANT-induced CTX can manifest as a sort of *cardiomyopathy*, referred to as *ANT-induced cardiomyopathy*, leading to HF, which limits the usability of the drugs, with important consequences for managing malignancies. ANT-related CTX represents a significant clinical burden, producing LV dysfunction in up to 9% of cases in a recent large prospective study (35). *Mechanisms of adverse effects:* ANT-related CTX mechanisms are derived from a combination of several cellular and molecular alterations leading to myocardial damage and dysfunction (Fig. 1). ANT-induced CTX is still not completely understood, though new insights on molecular mechanisms have been elucidated in recent years (373, 432, 435). The role of redox stress, resulting from an overproduction of ROS/RNS, in ANT-related CTX is undisputed (246, 247, 353, 434), although mechanisms are much less clear (see Section 10 for further details). ROS and RNS may be either direct or indirect inducers of the cardiac injury, but also triggers, byproducts of the injury or end-products arising from the injury itself. In addition, severity of oxidative/nitrosative stress often does not correspond well with the severity of the injury. This is connected to acceptance and explanation of poor efficacy of different antioxidants under relevant conditions. Recent data suggest that ANT-induced CTX is also strictly related to ANT interaction with topoisomerase 2 (Top2)- β in cardiomyocytes (229). Two types of Top2 enzymes are targeted by ANTs: Top2- α and Top2- β . While the former is present in rapidly dividing cells, such as cancer cells, and forms the ternary Top2-doxorubicin-DNA cleavage complex, inducing cell apoptosis, Top2- β is present in human cardiomyocytes, forming the Top2 β -doxorubicin-DNA complex, which causes DNA doublestrand breaks and transcriptome modifications, also leading to cell apoptosis (434). A seminal paper confirmed the crucial role of the Top2- β gene in an animal model, demonstrating that cardiomyocyte-specific deletion of the Top2- β gene is protective against ANT-induced damage (434). The DNA break caused by doxorubicin binding to Top2- β can therefore stimulate the DNA injury response. Consequently, the tumor suppressor protein p53, a fundamental enzyme for activating DNA repair proteins, can be induced. Unfortunately, p53 can also cause defective mitochondria biogenesis and metabolic failure by suppressing genes involved in organelle biogenesis, such as *peroxisome proliferator-activated receptor gamma coactivator 1-alpha* (PGC-1 α), and alteration of *oxidative phosphorylation* (OXPHOS) (434). Intriguingly, the metabolic perturbations induced by doxorubicin-activated p53 are responsible for altered autophagy, a process necessary for the normal recycling of dysfunctional mitochondria. Consequently, doxorubicin-damaged mitochondria accumulate in the cardiomyocytes, resulting in enhanced ROS/RNS generation and ultimately cell death. Recent observations in p53-null mice found a smaller impairment in cardiac functional reserve after ANT treatment, supporting this hypothesis (157). Interestingly, in these mice, mitochondrial and LV function were maintained

with increasing age, suggesting that p53-mediated inhibition of autophagy may play a role in all forms of cardiac dysfunction, not just doxorubicin-induced cardiomyopathy (157). Apart from p53, doxorubicin may also induce the mitogen-activated protein kinase (MAPK) pathway via ROS- and Ca^{2+} -dependent mechanisms (437). Importantly, extracellular signal-regulated kinases (ERKs), members of the MAPK family, may protect myocytes from apoptosis, while p38 MAPK induces death of cardiomyocytes (437). More studies are needed to elucidate the role of such kinases and of other less-characterized signaling pathways in ANT-induced cardiotoxicity. However, these data confirm that oxidative reactions, at the basis of ANT-induced LV dysfunction, are involved in most types of HF. Therefore, timely innovative pharmacological strategies that interfere with specific molecules involved in heart dysfunction (e.g. p53) may represent a potential common approach in limiting HF occurrence (250, 341). ANT-alcohol metabolites also play a pivotal role in inducing cellular injury and CTX via iron-dependent and -independent mechanisms. In fact, these metabolites disrupt iron and calcium homeostasis and, ultimately, lead to intracellular Ca^{2+} overload. Calcium overload has also been related to increased calpain proteolytic activity, which leads to cellular disarray and sarcomere disruption, resulting in sarcopenia (220). In addition, the interaction of ANTs with critical signaling pathways and with the activity of transcription factors may also explain sarcopenia, which derives from the limitation of sarcomere protein synthesis (165). Mitochondrial activity has a central role in ANT-induced CTX (257, 258). The presence of doxorubicin in the mitochondrion, due to a high affinity for the mitochondrial phospholipid *cardiolipin*, negatively affects its function, stimulating ROS/RNS production, inhibiting oxidative phosphorylation, and causing mitochondrial DNA damage (300), with a consequent progressive reduction of energy production leading to cell dysfunction (210). ANTs also appear to be responsible for mitochondrial calcium accumulation (300), leading to mitochondrial membrane injury. The mitochondrial pathway is an additional mechanism responsible for cellular intrinsic apoptosis. This involves elements of the outer mitochondrial membrane (OMM), including Bax and Bak, and activates cytochrome C and caspase, among others (257).

Some researchers have hypothesized that the loss of iron homeostasis and the Ca^{2+} overload caused by ANT alcohol metabolites, impairing cardiomyocyte energy and redox balance, could be sufficient to induce significant myocardial dysfunction, and that in addition, cardiac injury could be increased by an apoptotic loss of cardiomyocytes triggered by ROS and Fe^{2+} (257, 258). ANTs can also affect cardiac progenitor cells, hampering the regeneration capabilities of cardiac tissues following myocardial damage (158, 289). The controversy on the role of cardiac stem cells is discussed in Section 12. Finally, it should be noted that several factors can favor ANT-induced CTX, and this may explain the individual variability in CTX occurrence (246, 247) (Fig. 2). The so-called *multiple hit hypothesis* considers a late onset of CTX due to pharmacological and non-pharmacological subsequent injury. Therefore, strategies favoring cardiac adaptation to various stressors are crucial following ANT therapy (244). Of course, a better understanding of the molecular mechanisms of ANT-related CTX is essential in order to choose the best strategies to prevent and treat CTX (33, 231, 232, 345, 408). *Ways to reduce cardiovascular toxicity*: Several approaches have been proposed to reduce ANT cardiotoxicity, including ACE-inhibitors, β blockers, Doxrazoxane, PDE-5 inhibitors, Ranolazine and Statins, as well as nutritional supplementation and exercise training. The way the various approaches may reduce cardiovascular toxicity by ANT is treated in Sections 10 and 11.

3. ErbB2 inhibitors

ErbB2 (also called HER2) is a member of the human epidermal growth factor receptor family, which also includes ErbB1, ErbB3, and ErbB4. When bound by their ligands, these transmembrane receptors homodimerize or heterodimerize and are trans-phosphorylated, thus initiating several cellular responses. Until now, no specific ligand for ErbB2 has been identified, and the protein is believed to act as a dimerization partner of the other ErbBs (107). Importantly, ErbB2 is overexpressed in approximately 30% of breast cancer cases, and can then interact spontaneously with other ErbBs independently from ligand stimulation, thus triggering signaling pathways that stimulate tumor

growth and survival (361). *Adverse effects:* *Trastuzumab* is a humanized monoclonal antibody that binds the extracellular domain IV of HER/ErbB2 (107, 377). It is the prototypical anti-ErbB2 agent, and the first developed and most widely used type II cardiotoxic drug. Trastuzumab is particularly useful in treating ErbB2⁺ breast and gastric cancers. Unfortunately, it can also cause CTX in a substantial number of patients, peaking at 28% with concomitant administration of trastuzumab and ANTs (262, 362, 377). Indeed, as said, ANTs are responsible for type I CTX with permanent cardiac damage. Therefore, reduced left ventricle ejection fraction (LVEF) results from the association of trastuzumab and doxorubicin: Trastuzumab enhances or even induces doxorubicin toxicity. Once anti-ErbB2 agents block the protective mechanisms of ErbB2, the oxidative damage induced by doxorubicin increases (91). This co-administration is now avoided. As a class II cardiac dysfunction (93, 94), trastuzumab CTX appears to be elicited by the impairment of contractility rather than the loss of cardiomyocytes, and previous chemotherapy seems to be responsible for the troponin release observed in sequential treatment (91). *Pertuzumab* is a more recent anti-HER2 antibody that binds the receptor's domain II. *Lapatinib* is a different anti-ErbB2 agent, a small-molecule inhibitor of the intracellular tyrosine kinase domain of ErbB2. Of note, trastuzumab only disrupts ligand-independent ErbB2 signaling, while pertuzumab interferes with the formation of ligand-induced ErbB2 heterodimers. In contrast, lapatinib inhibits both ligand-induced and ligand-independent ErbB2 signaling (69). Interestingly, lapatinib seems to be less toxic than trastuzumab. Data regarding the toxicity of pertuzumab are more limited (262).

Mechanisms of adverse effects: Cardiotoxicity of anti-ErbB2 drugs has been attributed to the inhibition of fundamental actions of neuregulin 1 in the heart (262, 286). In brief, in response to various stimuli, including mechanical strain, adult cardiac microvascular endothelial cells may release neuregulin 1 (NRG1, especially the NRG1 β isoform) (221). Thus, NRG1 acts on cardiomyocytes in a paracrine manner, triggering ErbB4/ErbB4 homodimerization and ErbB4/ErbB2 heterodimerization to stimulate protective pathways in response to stress (221, 286). The ErbB2 pathway mediates cell survival and functionality, with recent data focusing on its role in mammalian heart regeneration (63), and appears to be stimulated when the heart experiences adverse hemodynamics or other stress, such as ANT therapies (Fig. 3) (110). It has been postulated that by interfering with the NRG1/ErbB4/ErbB2 axis in the myocardium, anti-ErbB2 agents can cause cardiomyocyte damage and eventually HF, and that this is more likely to occur if myocytes are concomitantly exposed to other stressors, such as hypertension or doxorubicin (70, 91). Supporting such a hypothesis, ErbB2 cardiac KO-mice exhibited dilated cardiomyopathy, with increased susceptibility to ANT-induced damage to cardiac myocytes (61, 291). Conversely, overexpression of ErbB2 in the heart resulted in lower levels of ROS in mitochondria, with reduced ROS levels and less cell death in neonatal myocytes isolated from ErbB2(tg) hearts after doxorubicin treatment, due to enhanced levels of glutathione peroxidase 1 (GPx1) protein and GPx activity, with higher levels of two known GPx activators, c-Abl and Arg. These data suggest new mechanisms by which ErbB2 blockers can damage heart structure and function (19).

These data have led to further studies on NRG1/ErbB4/ErbB2 that have focused away from chemotherapy-induced HF to heart disease from any cause, with implications for new therapeutic perspectives. For example, in mice subjected to pressure overload, ErbB4 and ErbB2 (both mRNA and protein) decreased significantly with the progression of the disease from compensated cardiac hypertrophy to overt HF (250, 325). Consistently, ErbB2 and ErbB4 receptor expression and activation/phosphorylation were observed to be lower in human failing myocardia, compared with organ donors (326). Interestingly, LV unloading by implantation of an LV assist device restored the levels of ErbB4 and ErbB2 (326, 400). In an apparent contrast with these results, dogs with pacing-induced HF showed increased phosphorylation of ErbB4 and ErbB2 (78). Inactivation of the intracellular downstream effectors of ErbB4 and ErbB2, ERK1/2 and Akt, was observed, suggesting a disabled NRG1/ErbB4/ErbB2 signaling. Actually, NRG1 expression is increased in HF compared with control conditions in most studies (78, 250, 326). All in all, these data hint that deranged NRG1/ErbB4/ErbB2 activity is involved in the pathophysiology of HF in at least two manners: *i*) HF

may derive from the use of anti-ErbB2 drugs, such as trastuzumab; *ii*) ErbB4/ErbB2 is downregulated and/or uncoupled from intracellular signaling despite normal or increased NRG1, possibly leading to cardiac decompensation (250). Furthermore, novel observations suggest that levels of catecholamines, that usually increase with the occurrence of LV dysfunction and with ANT administration (176, 250, 282), can stimulate ErbB2 expression in myocytes, thus making these cells particularly susceptible to the effects of trastuzumab, resulting in myocardial toxicity (382).

Ways to reduce cardiovascular toxicity: The aforementioned experimental results may support the use of β blockers in the prevention of trastuzumab CTX (see below) (281), in line with a retrospective study that found that continuous use of β blockers was associated with lower risk of new HF events in subjects on trastuzumab, ANTs, or both (347). Prevention with β blockers is currently being assessed in clinical trials (180, 281, 347, 349) with bisoprolol (MANTICORE 101-Breast) (305), NCT01009918 (carvedilol), and NCT01434134/NCT00806390 (metoprolol) to cure or prevent trastuzumab-induced LV dysfunction (250, 281). Interestingly, from the recent PRADA (prevention of cardiac dysfunction during adjuvant breast cancer therapy) trial, we can infer that blocking only β_1 with metoprolol may not produce an adequate and sufficient cardioprotection (128), thus supporting the use of non-selective β_1 and β_2 blockers (382). In the clinical setting of trastuzumab-induced cardiac dysfunction, when trastuzumab is discontinued, normal ErbB2 signaling is restored, and the reduced LVEF can increase back to normal levels. Indeed, trastuzumab re-administration after discontinuation is considered relatively safe upon LVEF recovery (93, 94). Animal studies have demonstrated that NRG1 regulates doxorubicin injury in rat myocytes (390). Owing to the aforementioned cardioprotective properties of NRG1 via ErbB4/ErbB2, and as the activity of these receptors is altered in HF, the axis neuregulin-ERB is now being intensively investigated in clinical trials for HF treatment (111, 112, 221). It has been hypothesized that NRG1 and NRG1 analogs can be used as therapeutic agents in HF. Intravenous administration of recombinant human NRG1 and of the glial growth factor 2 (GGF2) isoform of NRG1 β enhanced heart function and reduced LV dimensions in experimental failing heart (111, 112, 218, 227, 250). Since NRG1 exerted positive effects in animal models of ischemia-induced HF even when administered after acute myocardial infarction, it can be speculated that it is able to produce beneficial reverse remodeling of the damaged heart, and does not simply limit cardiac dilation (111, 112, 227). Also, it appears that NRG1 exerts an antifibrotic effect, directly inhibiting cardiac fibroblasts, thus preventing fibrosis (111, 112).

Clinical studies have demonstrated that recombinant human NRG1 is well-tolerated by patients, and ameliorates cardiac dimensions and LVEF until up to 3 months after treatment (116, 169). Nevertheless, NRG1 may be a growth factor for tumor cells, particularly when administered systemically. Hopefully, additional experimental and clinical studies can assess this fundamental safety concern, producing novel data concerning the effects of NRG1 in HF (221, 250).

4. Vascular endothelial growth factor (VEGF) inhibitors and multi-targeted kinase inhibitors

Adverse events: Anti-angiogenic drugs disrupt the VEGF signaling cascade (Fig. 4) and may induce type II CTX (Fig 5). VEGF is a modulator of myocardial function and growth, while at the same time modulating the integrity and expansion of the coronary and systemic blood vessels (43, 44, 62, 88, 103, 104, 107, 240, 392). VEGF antagonists may therefore produce different forms of CTX, mainly hypertension, thromboembolism, LV dysfunction, and HF (126, 344, 421).

In particular, *bevacizumab*, *sorafenib*, and *sunitinib* are now widely used for the treatment of different cancers. More recently introduced TKIs can also induce CTX. *Regorafenib* is a multi-target TKI whose targets include VEGF receptor (VEGFR) 1-3, endothelial-specific receptor tyrosine kinase (trk2), PDGFR, fibroblast growth factor receptor (FGFR), cKIT, RET, and rapidly accelerated fibrosarcoma (RAF) kinase. Regorafenib is used in the treatment of colorectal tumors and gastrointestinal tumors (28). It may be responsible for arterial hypertension; less frequently, it can produce cardiac ischemia and myocardial infarction (30). *Pazopanib* and *axitinib*, used in the treatment of metastatic renal tumors, are also associated with a high rate of arterial hypertension. Pazopanib is an orally administered multi-targeted TKI, targeting VEGFR 1-3, PDGFA and PDGFB

receptors, and c-KIT. In a recent study, the frequency of pazopanib-associated hypertension varied between 36% and 46% (268). Axitinib is a third-generation VEGFR inhibitor used in metastatic renal cancer after failure of previous treatments, and is very selective. In a study comparing axitinib and sorafenib, the frequency of hypertension was 29% for sorafenib and 40% for axitinib (162). New anti-angiogenic drugs not yet approved for clinical use are *vatalanib* and *nintedanib*. Preliminary evidence indicates a potential risk of arterial hypertension and congestive HF and, for vatalanib, of pulmonary embolism, although more rarely (318, 407). *Mechanisms of adverse effects:* The myocardium requires appropriate perfusion to function properly (43, 44, 62, 88, 103, 104, 107, 240, 392), and depends on HIF-1 and VEGF pathways, similarly to tumors. Of note, inhibition of HIF-1 by p53 may produce HF during chronic pressure overload (336). Moreover, conditional expression of a VEGF scavenger may cause myocardial hibernation and microvessel rarefaction, which can be reversed by suppressing the expression of the scavenger, even months after its induction (244, 417). Such findings show that the myocardium is very sensitive to anti-angiogenic treatments, especially with hypertension-related pressure overload. The antibody *bevacizumab* binds circulating VEGF-A, which triggers signaling in endothelial cells, and is used as a therapy for advanced lung, breast, and colon/rectum cancers (160, 334). It has been observed that bevacizumab can induce cardiac dysfunction in 1% of chemotherapy-naïve patients and 3% of patients with previous chemotherapy (256). *Sunitinib* and *sorafenib* are small-molecule tyrosine kinase inhibitors (TKIs), and are approved for treating metastatic renal cancer and imatinib-resistant gastrointestinal stromal tumors (GISTs) (45, 126). Importantly, they are not highly selective, and can inhibit kinases other than VEGF (43). In particular, *sunitinib* interferes with more than 30 other tyrosine kinases, including platelet-derived growth factor receptor (PDGFR) alpha and beta, the REarranged during transfection (RET) proto-oncogene, FMS-related tyrosine kinase 3 (FLT3), c-Kit, and colonystimulating factor 1 receptor (CSF1R) (43, 107, 135, 230). This explains why sunitinib is considered more cardiotoxic than other anti-angiogenic drugs, with an incidence of LV dysfunction in up to 28% of patients (51, 187, 269, 387) (Fig. 5). Indeed, all these kinases play a role in the maintenance of CV function (9, 168, 217, 228). The high CTX of sunitinib is also due to interference with off-target kinases, such as ribosomal S6 kinase (RSK), with consequent activation of the intrinsic apoptotic pathway, and 5' AMP-activated protein kinase (AMPK, involved in the response to energy stress), with exacerbation of ATP depletion (107, 186). Interestingly, Hasinoff et al. (135) confirmed the inhibition of AMPK in isolated cardiomyocytes, but also suggested this is likely not essential for the development sunitinib cardiotoxicity. Creatine kinase (CK) may be also involved in the modulation of sunitinib contractile actions (393). A study (51) in mice treated with sunitinib also showed a prolonged opening of the non-selective mitochondrial permeability transition pore (mPTP) and a significant mitochondrial swelling with deformation of the normal mitochondrial architecture in myocytes from heart subjected to pressure overload. Other studies (422) showed that sunitinib likely does not induce significant impairment of oxidative phosphorylation, thus the impact of sunitinib on energy metabolism is still controversial, with the incidence of sunitinib-induced myocardial dysfunction being perhaps lower than initially suggested. Additionally, a 2013 manuscript (46) pointed attention from cardiomyocytes to microvascular dysfunction in the heart and pericyte damage as another important mechanism of cardiotoxicity induced by sunitinib. *Sorafenib* appears to inhibit at least 15 kinases, including the VEGF receptor, PDGFR, Raf-1/B-Raf, FLT3, and c-Kit (43, 107, 392). The incidence of sorafenib-induced CTX is not yet fully characterized. In two meta-analyses that included almost 7,000 patients treated with sunitinib and 900 patients treated with sorafenib, rates of 4.1% for sunitinib-induced HF and 1% for sorafenib-associated cardiac dysfunction were shown (77, 321), but most of these observations were derived from retrospective analyses; only a few trials have assessed LV dysfunction prospectively. The work of Schmidinger and collaborators (344) showed that three in 14 patients who were administered sorafenib and had cardiac events exhibited abnormal LVEF. Recently, Feng and coworkers (98) observed that the axis between the brain-derived neurotrophic factor (BDNF) and a tyrosine kinase receptor (TrkB) is a key player in the regulation of myocardial excitation-contraction coupling, independently and in parallel to G protein-coupled receptor (GPCR)

signaling. These data further support the concept that tyrosine kinase blockade with antineoplastic treatments can interfere with fundamental signaling, thus impairing cardiac mechanical work that may produce LV dysfunction (106). *In summary*, several mechanisms may lead to cardiac dysfunction in patients treated with anti-VEGF therapy: cKit inhibition, altered activation of MAP with consequent alteration of energy production and mitochondrial function, PDGFR inhibition, and inhibition of signaling favoring cell survival, as well as angiogenesis inhibition and induction of arterial hypertension. Importantly, hypertension is a main side effect of all three major anti-VEGF drugs (272). *Mechanisms of arterial hypertension* include both functional (inactivation of endothelial nitric oxide synthase and production of vasoconstrictors such as endothelin-1) and anatomic (capillary rarefaction) modifications, that lead to vasoconstriction and an increase in peripheral vascular resistance (272, 277, 353). The main mechanisms of capillary rarefaction are considered the loss of pericytes due to PDGFR inhibition, along with inhibition of angiogenesis by VEGFR inhibition (353). Moreover, renal dysfunction due to angiogenesis inhibition can play a role in inducing and maintaining arterial hypertension. All said, mechanisms of hypertension induced by antiangiogenic drugs have not been fully elucidated yet, and are still an unresolved issue.

Bevacizumab produces severe hypertension that, at least in some circumstances, is not reversed by discontinuing the drug. Hypertension from anti-angiogenic agents has been suggested to be a biomarker of anti-cancer drug efficacy, because some patients who developed hypertension were observed to survive longer than those who did not (122). It has been shown that in cases of metastatic colorectal cancer, 20% of patients showed grade 2-3 hypertension. A partial remission was observed in 75% of subjects with bevacizumab-induced hypertension, and in only 32% of those with no hypertension. Moreover, patients who showed grade 2-3 hypertension had significantly longer progression-free survival than non-hypertensive patients (342). *Sunitinib* can also cause hypertension, with an incidence ranging from 5% to 47% in different studies. Sunitinib was shown to induce hypertension ($\geq 150/100$ mmHg) in 47% of the subjects studied, with grade 3 hypertension seen in 17%. High blood pressure was observed within the first 4 weeks of therapy (32, 270).

Inhibition of VEGF signaling can also cause *arterial and venous thrombosis*. Arterial thromboembolic events (ATE) are mainly related to VEGF inhibition and consequent impairment of vascular homeostasis due to reduction of *nitric oxide* (NO) synthesis, endothelial dysfunction, and production of vasoactive mediators that favor plaque instability and thrombus formation (211). *Bevacizumab* causes ATE more frequently in patients contemporaneously treated with other chemotherapeutic agents, in older patients, and in those who have experienced previous thrombotic events (315). The real burden of venous thromboembolism related to *bevacizumab* is less clear (161). The pathogenesis of venous events is always related to impairment of vascular homeostasis due to VEGF inhibition and to production of proinflammatory cytokines that favor activation of the coagulation cascade (144). Sorafenib, pazopanib, and axitinib may also increase the risk of ATE. In a meta-analysis of 10,000 patients, the incidence of ATE was 1.7% in sorafenib-treated patients (49). Venous thrombotic events were reported in 3% of axitinib-treated patients, with ATE in 2% and transient ischemic attack in 1%. However, HF was observed in less than 1% of subjects treated with sorafenib and 3% of patients treated with pazopanib (324). Cardiac ischemia or myocardial infarction can also occur with sorafenib (3.8%), pazopanib (2%), and axitinib ($<1\%$) (30). This is mainly related to inhibition of VEGF signaling, leading to endothelial dysfunction, vasoconstriction, and microvascular rarefaction. Moreover, a reduction in VEGF levels creates an imbalance between cell survival and apoptosis. Endothelial cell apoptosis favors an exposure of sub-endothelial collagen and activation of the coagulation cascade, while reduced VEGF levels also interfere with the platelet-mediated fibrinolytic cascade (211). Finally, patients treated with sorafenib, pazopanib, and vandetanib can present an electrocardiogram (ECG) with *QT interval prolongation*, which predisposes to an enhanced risk of ventricular arrhythmias (194, 214). In particular, sorafenib can frequently induce QT prolongation (40.5%), thus greatly increasing the risk of ventricular arrhythmias (30). Vandetanib has also been related to a moderate risk of QT prolongation (16%), and more rarely life-threatening arrhythmias; in addition, it is associated with enhanced risk of arterial

hypertension (24%) and HF (21%) (434). In patients treated with pazopanib, the risk of QT prolongation and *torsade de pointes*, a dangerous polymorphic ventricular tachycardia leading to sudden cardiac death, is less than 2% (303).

In patients receiving drugs potentially interfering with QT duration, electrocardiographic monitoring of QT interval and periodic control of electrolytes are recommended. A reduction in the drug's dose can be warranted, but rarely discontinuation. Particular attention should be paid to patients with personal or familial history of QT prolongation or those who are under concomitant medication that can influence QT interval. For further details on the approaches to reduce cardiovascular toxicity, see Sections 10 and 11.

5. Tyrosine kinase inhibitors (TKIs) and anti-BCR-abl agents

Chronic myeloid leukemia (CML) is a cancer of the white blood cells resulting from the clonal expansion of a transformed multipotent hematopoietic stem cell. It is characterized by a reciprocal translocation between the long arms of two chromosomes, namely chromosomes 9 and 22. This translocation produces a shortened chromosome 22, the so-called *Philadelphia chromosome*. The consequence of such translocation is the production of the BCR-ABL1 fusion gene on chromosome 22, and the reciprocal ABL1-BCR gene on chromosome 9. While the latter does not have any functional role in CML, the BCR-ABL1 fusion gene is necessary for CML pathogenesis. While the ABL1 tyrosine kinase is a master-regulator of the cell cycle regulation, the BCR-ABL1 fusion gene generates a constitutively active tyrosine kinase that leads to uncontrolled proliferation (332).

Targeting the BCR-ABL1 fusion gene has revolutionized the management of CML, turning a fatal disease into a chronic disorder that in most cases is compatible with a normal lifespan (339). Based upon the data from the IRIS study, which documented a dramatic improvement in survival, imatinib was the first targeted drug approved for the therapy of CML (285).

However, because of the development of a point mutation in the BCR-ABL1 fusion gene, a considerable number of patients may acquire resistance to imatinib (10). Second-generation TKIs - dasatinib, nilotinib, and bosutinib - have been shown to be effective in imatinib-resistant patients, and more rapid in achieving a deep molecular response (57, 182, 383).

Ponatinib, a third-generation TKI specifically designed to overcome resistance caused by a T315I mutation in BCR-ABL1 kinase, has exhibited high clinical efficacy in patients with multi-TKI-resistant CML (56). At their debut in the clinical arena, all five drugs appeared cardiologically safe; however, subsequent information indicated that they may exert adverse CV side effects which may affect prognosis and quality of life and must be taken into account when selecting treatment agents (266). All these drugs demonstrate significant off-target bindings and off-target effects, which may contribute to both toxicities and therapeutic control of the myeloproliferative disorder (124, 383).

Imatinib was originally developed as a PDGFR inhibitor. It is a first-generation TKI that binds to the tyrosine kinase ABL while the protein is in the closed conformation and is inactive. It also inhibits other TKs, including VEGFR members and KIT family kinases (124).

Imatinib adverse events: A 5-year follow-up study on patients with newly diagnosed CML treated with imatinib showed an excellent CV safety record for the drug (285). However, Kerkela et al. reported clinical data from 10 patients with normal ventricular function who developed severe cardiac dysfunction and New York Heart Association (NYHA) Class 3-4 HF after imatinib treatment, and demonstrated that mice treated with imatinib develop a severe form of LV contractile dysfunction (185). The publication by Kerkela et al. prompted many hematologists who had used imatinib to treat multiple patients to review their clinical database; the rates of CTX found were extremely low (16, 113, 138, 329). Further clinical studies then confirmed the excellent CV risk profile of imatinib (54, 60, 64, 80, 90, 148).

Mechanisms of imatinib-induced adverse events: Several studies investigated the mechanisms responsible for cardiac toxicity, and found that imatinib-induced ABL inhibition leads to alterations in the endoplasmic reticulum (ER) stress response by activating the IRE1 kinase

arm of the response. IRE1 activates apoptosis signal-regulating kinase 1 (ASK1) and c-Jun Nterminal kinase (JNK), which in turn causes inhibition of antiapoptotic Bcl-2 (B-cell leukemia/lymphoma) and cytochrome c release from mitochondria, thus leading to mitochondrial function impairment and cell death (43, 44). The inhibition of Abl kinase by imatinib is also responsible for PRKR-like endoplasmic reticulum kinase (PERK) activation, which results in impaired protein import in the mitochondrial matrix, inducing mitochondrial death pathways (409).

Other than the potential proapoptotic effect on cardiomyocytes, imatinib has been shown to exert a number of cardiologically relevant effects. First, it causes fluid retention and edema that may contribute to a mistaken diagnosis of HF. This is probably due to imatinib's inhibition of PDGFR (356). Paradoxically, imatinib treatment can also protect against brain and lung edema during stroke and lung injury, respectively (39, 374). It has been demonstrated that in human endothelial cells pre-treated with a variety of barrier-disruptive agents, imatinib reduces endothelial barrier dysfunction via inhibition of the abl-related gene (7, 47). Imatinib also has favorable effects on glucose control by improving both beta cell function and peripheral insulin sensitivity (101, 130). Imatinib improves hemodynamics and reverses vascular remodeling and cor pulmonale in pulmonary arterial hypertension by PDGF inhibition (343). Finally, imatinib was found to attenuate myocardial remodeling and improve LV diastolic dysfunction in spontaneously hypertensive rats by affecting the PDGRF pathway without the blood pressure-lowering effect (170).

Nilotinib is a structural analog of imatinib, which binds and potentially inhibits PDGFR and KIT family kinases, but not kinases of the SRC group (124). It is approved for the therapy of subjects with newly diagnosed Ph⁺ CML in any phase. Nilotinib is also approved for CML patients resistant to or intolerant of previous therapies, including imatinib.

Nilotinib adverse events: Early in the development of Nilotinib there was evidence of QT prolongation, leading to a warning to perform serial ECGs, prevent and correct electrolyte abnormalities, and avoid concomitant drugs potentially responsible of QT interval prolongation (182). However, subsequent trials found no alarming signals of QT-related ventricular arrhythmias (266). Clinical trials, as well as studies analyzing real-life settings, found that nilotinib exacerbates the glycometabolic and lipid profile (26, 166, 167, 266, 313, 317). Over the past 5 years, several clinical trials, retrospective studies, meta-analyses, and postmarketing surveillance studies have shown that nilotinib-treated patients are at increased risk of CV events, especially those related to peripheral artery disease (2, 54, 64, 80, 118, 148, 190, 209, 266, 403). Oddly, these vascular adverse events were not reported during the first clinical studies.

Mechanisms of nilotinib-induced adverse events: Recent studies have documented a number of nilotinib-induced effects on endothelium, platelets, and coagulation, which, together with the metabolic effects, enhance the risk of vascular adverse events (4, 22).

As for myocardial toxicity, clinical studies have shown that nilotinib does not cause ventricular dysfunction. This finding concurs with experimental data showing that nilotinib and imatinib produce little or no damage to cardiomyocytes, in comparison with dasatinib, bosutinib, and ponatinib (137).

Dasatinib is a second-generation TKI, and more potent than imatinib. Unlike imatinib and nilotinib, dasatinib binds to TKs, both in their active and inactive conformational state. It is classified as a dual Abl/Src inhibitor, although it inhibits a broad spectrum of receptor kinases, including c-Kit and PDGFR (124).

Dasatinib is approved as a frontline therapy of Ph⁺ CML patients in the chronic phase, and for salvage treatment of Ph⁺ CML or Ph⁺ acute lymphoblastic leukemia (ALL) patients who are intolerant of or resistant to other TKIs.

Dasatinib adverse events: For years, the CV safety profile of dasatinib was considered similar to that of imatinib, with the exception of pleural effusion, which has been observed since the

first use of the drug (383). Clinical studies with a long follow-up period found that pleural effusion occurs in one of every three patients, and that half of pleural events occur within the first 2 years of therapy. Pleural effusion requiring drug discontinuation occurs in less than 10% of the cases (351).

Pulmonary arterial hypertension (PAH) is a rare but serious complication of dasatinib treatment. A transient significant increase of pulmonary arterial pressure detected by echocardiography was observed for the first time in 2017 among patients with pleural effusion (312). Subsequently, other reports emerged of PAH not associated with pleural effusion (263).

In clinical studies, PAH has been observed in 5% of subjects on dasatinib as a frontline therapy for 5 years and in 2.4% of patients treated with dasatinib for 7 years, who were resistant to or intolerant of other treatments (351). A recent assessment of all causes of dasatinib-related PAH confirmed by catheterization (41 patients) showed that a unique feature of dasatinib-induced PAH is different complete or partial reversibility upon drug discontinuation (352). However, the French PH Registry that identified nine cases of dasatinib-associated PAH reported that most patients did not experience complete recovery, and recorded two cases of cardiac death following dasatinib withdrawal (263).

Analysis of the FDA database designed to support postmarketing surveillance found that PAH was associated with dasatinib and not with other TKIs, and often occurred in patients with CV risk factors or a medical history of cardiopulmonary events (54).

Mechanisms of dasatinib-induced adverse events: Pleural effusion is considered the result of PDGFR inhibition, particularly of the PDGFR- β isoform, of which dasatinib is the most potent inhibitor; however, other mechanisms have been suggested (184). Due to the high frequency of lymphocytes in pleural fluid and tissue and the association with skin rash or history of autoimmunity, an autoimmune mechanism has been hypothesized (297). It has been suggested that an immune-mediated mechanism underlying the occurrence of pleural effusion could help to promote tumor regression. Patients who develop lymphocytosis and increased levels of specific lymphocyte subsets in association with pleural effusion have a higher major molecular response (MMR) rate and better progression-free and overall survival than patients who do not (89).

The underlining molecular mechanism responsible for PAH is still poorly understood. Since dasatinib is a potent pan-Src inhibitor, it has been suggested that Src inhibition is pivotal in the development of PAH (264). The evidence that CML patients treated with dasatinib may display high circulating levels of E-selectin, intercellular adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM), and the observation that cultured pulmonary endothelial cells administered with dasatinib display an increased mitochondrial ROS production and apoptosis, support the notion that dasatinib-induced PAH is caused by endothelial dysfunction (127).

Because vascular events have been described in patients treated with other TKIs, recent clinical trials have evaluated the incidence of coronary, cerebral, and peripheral thrombotic events in dasatinib-treated patients; a slightly higher risk was found, compared with imatinib. However, a recent meta-analysis showed that the use of dasatinib is associated with a significant increase in the risk of CV events. In a population-based cohort study, the incidence of myocardial infarction was 2.4 higher in patients treated with dasatinib than in those treated with imatinib.

Bosutinib is a second-generation, dual Src/Abl TKI, lacking significant PDGFR or c-KIT binding properties (124). Bosutinib is currently approved only for patients with Ph1 chronic phase CML who were resistant to or intolerant of previous TKI therapy.

Bosutinib adverse events: Studies that evaluated bosutinib enrolled patients newly diagnosed with CML, or patients resistant to or intolerant of other TKIs; these studies documented a low

incidence of cardiac and vascular events (31, 55, 57, 58). Similarly to other TKIs, the incidence of adverse events was higher in second- or later-line treatment compared with firstline treatment. HF and coronary or peripheral artery disease-related events were rare, suggesting that the cardiotoxic profile of bosutinib differs from that of other second- or thirdgeneration

TKIs. Most events occurred within the first year of therapy, and very few patients discontinued treatment because of these events, which were mostly managed with concomitant medications (55).

It should be noted that in a first-line setting, the overall incidence of events and dose reduction or interruption is similar for imatinib and bosutinib, even though pericardial disorders occurred more often in bosutinib-treated patients than in those treated with imatinib.

Ponatinib, a third-generation BCR-ABL TKI, was originally developed for the inhibition of pan-resistant ABL TK, and is clinically effective in imatinib-, nilotinib-, and dasatinib-resistant CML. Ponatinib targets BCR-ABL in its inactive conformation and inhibits T315I and other BCR-ABL mutants. It also targets a broad spectrum of TK receptors, including EGFR, PDGFR, VEGFR, SRC kinase, c-KIT, FLT3, and RET (124).

Ponatinib adverse events: Ponatinib was tested in Ph⁺ patients with refractory CML or ALL enrolled in phase I (65 patients) and in phase II (449 patients) of the PACE trial. Both studies documented a high efficacy of the drug, accompanied by an increased risk of arterial thrombotic events (56, 59). For these reasons, ponatinib was approved with a warning of the risk of serious vascular events. Findings from these studies provided the rationale to perform a phase III study (EPIC) to test the hypothesis that ponatinib may lead to a deep molecular response in patients newly diagnosed with CML, and to assess its safety in patients with no previous exposure to other TKIs (226). The extended follow-up periods of the phase I and II studies documented that cardiac, cerebral, and peripheral thrombotic events continued to occur; this finding determined the early termination of the phase III study and led ARIAD Pharmaceuticals and the FDA to withdraw ponatinib from the market in October 2013. In January 2014, after a reassessment of the benefit/risk ratio of ponatinib, the FDA allowed its reintroduction into the market, with a recommendation to take appropriate measures to mitigate adverse effects in patients. The mechanisms of ponatinib CV toxicity are still poorly understood. Diagnostic and pharmacological measures aimed at reducing the CV risk were not included in the protocols of the phase I-III trials. The implementation of these preventive measures may help to improve the therapeutic index of ponatinib in the clinical setting (27). For further details on the approaches to reduce TKIs-induced CTX, please refer to Sections 10 and 11.

6. Taxanes

Adverse effects: Although the potential of taxanes to induce cardiac dysfunction has been likely overestimated in the past, they deserve a brief note. The most commonly used taxanes are docetaxel and paclitaxel, which are still used in breast, non-small cell lung and ovarian cancers. Among adverse effects of these drugs, a high incidence of arrhythmias has been observed, including asymptomatic sinus bradycardia (330), which usually is not a major problem for patients. A large range of conduction blocks and cardiac ischemia have been also observed in a few patients participating in trials (330). Ventricular arrhythmias are far less common: only 0.26% of patients experienced ventricular tachycardia, and ventricular fibrillation, and many of them were also co-treated with cisplatin (245, 330). In a clinical trial (EORTC 24971/TAX 323 Study Group) patients treated with docetaxel, displayed a 1.7% incidence of cardiac ischemia (411). In about 3500 patients treated with paclitaxel followed by the Cancer Therapy Evaluation Program's Adverse Drug Reaction database, the overall incidence of severe (grade 4 and 5) cardiac events was less than 0.3% (12). These severe events were observed up to 2 weeks after the beginning of paclitaxel treatment. Of note, many of these subjects had important cardiovascular risk factors, including coronary disease and

hypertension.

Mechanisms of adverse effects: Taxanes exerts anticancer effects acting as anti-microtubule agents and fostering polymerization of tubulin. In this way, these agents induce microtubule dysfunction and alter cell division. Moreover, they may affect histamine release (330). These taxane-induced effects may perturb cardiac function. Brady-arrhythmias may be due to stimulation of histamine H₁ and H₂ receptors. The latter receptors may increase the possibility of reentry of depolarization, which is at the basis of ventricular ectopy (245, 330). Ischemia and increased myocardial oxygen demands render the heart more susceptible to arrhythmias. Of note, paclitaxel in combination with anthracyclines increases the incidence of CTX, which appears at lower cumulative doses with respect to anthracyclines alone (120). In particular, plasma levels of doxorubicin and the formation of the toxic metabolite doxorubicinol in myocytes can be enhanced by taxanes.

Ways to reduce cardiovascular toxicity: Cardiotoxic symptoms are frequently resolved upon discontinuation of taxanes. Since histamine is considered as a relevant player in taxane CTX, treatment with corticosteroids and antihistamines may reduce the incidence of clinically significant arrhythmias (245, 330).

7. Cancer immunotherapy

All components of the innate and adaptive immune system are important in the recognition and elimination of tumor cells (immune surveillance) (133). These immune components recognize specific neo-antigens expressed by tumor cells. However, the production of immunosuppressive cytokines/chemokines, the presence of immunosuppressive cells, or the expression of inhibitory checkpoints within the tumor microenvironment, allow the tumor cells to escape immune surveillance (296).

Immune Checkpoint Inhibitors: Tumors exploit immune checkpoints to evade antitumor immunity. The success of cancer immunotherapy over the past decades has revolutionized the management of a wide array of malignancies. At the forefront of immunotherapy are immune checkpoint blockers, which have seen unprecedented success in cancer treatments because of their broad bioactivity across many tumor types. The two most prominent to date are the targeting of cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and the interaction between the proteins programmed cell death 1 (PD-1) and programmed death-ligand 1 (PDL1). *CTLA-4:* It has structural homology to the co-stimulatory molecule CD28, and can also bind B7 molecules on antigen-presenting cells (APCs) with higher affinity than CD28. CTLA-4 is a competitive antagonist of the CD28-B7 interaction in that it blocks co-stimulation at the T cell-APC interaction, thus suppressing activation of its cell response (200) (Fig. 6). *Ipilimumab and Tremelimumab* are monoclonal antibodies for clinical use against CTLA-4 (117, 354, 355, 431).

PD-1/PD-L1 Pathway: PD-1 is a checkpoint receptor that, by binding with its ligands (either PD-L1 or PD-L2), inhibits T effector functions by dampening signaling downstream of the T cell receptor (TCR) (397). Therefore, the expression of PD-L1 in the tumor microenvironment protects cancer cells from immune-mediated destruction. Several monoclonal antibodies against the PD-1/PD-L1 axis have been developed and/or approved as anti-cancer agents (396, 397).

PD-1, like CTLA-4, is expressed in activated cells, and its activation downregulates signaling mediated on antigen recognition by the TCR (354). PD-1 has two ligands, PD-L1 and PD-L2. PD-L1 can be expressed in many cell types, including tumor cells, immune cells, epithelial cells, and endothelial cells (354). PD-L2 is predominantly expressed in APCs. *Pembrolizumab* and *Nivolumab* are PD-1-blocking monoclonal antibodies approved for treating different types of cancers. *Atezolizumab* is a PD-L1 targeted monoclonal antibody recently approved for treatment of certain tumors (354). Other inhibitory molecules (e.g. LAG3, OX40, TIM3, TIGIT) are being assessed for their potential utility as immunotherapeutic targets (15, 211, 279, 399).

Combination of checkpoint inhibitors: CTLA-4 or PD-1/PD-L1 blockade as a monotherapy has shown impressive tumor regression in some patients with different solid and hematological cancers (95, 225, 241); however, the overall long-term survival rate should be improved (304). Ongoing clinical trials combine different checkpoint inhibitors. In addition, some clinical trials combine checkpoint inhibitors with angiogenesis inhibitors (i.e. bevacizumab), epidermal growth factor receptor (EGFR), TKIs or BRAF inhibitors, and chemotherapy or radiation therapy (396). *Checkpoint inhibitors and immune-related adverse events:* Checkpoint inhibitors can cause a

novel spectrum of adverse events called immune-related adverse events (IRAEs) (254, 420), because they can induce autoimmune manifestations (75, 202). The most common IRAEs following treatment with CTLA-4 inhibitors include rash, diarrhea, colitis, hepatotoxicity, and endocrinopathies (115, 149). Immune-mediated CTX produced by these compounds has generally been observed in individual cases with variable presentations, comprising pericarditis and myocarditis (117, 141, 414, 431). The largest case series to date describing CTX following treatment with checkpoint inhibitors reported seven cases (141).

Monoclonal antibodies targeting PD-1 (such as pembrolizumab, nivolumab, and pidilizumab) or PD-L1 (atezolizumab, durvalumab) have shown a favorable toxicity profile in several trials (82). However, occasional reports of myocarditis after nivolumab (151) or pembrolizumab (207) treatment have been reported.

Although so far, there have been few case reports on cardiac adverse effects in patients treated with checkpoint inhibitors, several notes of caution should be considered. First, experimental data in PD-1-deficient mice are associated with dilated cardiomyopathy and sudden death by congestive HF (280, 288). In addition, PD-1 protects against inflammation in T cell-mediated myocarditis (385). Finally, PD-1 deficiency leads to the development of fatal myocarditis in mice genetically predisposed to autoimmunity (418). The latter observation is particularly important because patients with underlying autoimmune disorders have always been excluded from clinical trials with checkpoint inhibitors. Therefore, the real-life risk of cardiac adverse events in patients with autoimmune disorders treated with checkpoint inhibitors is so far unknown. Checkpoint inhibitors have only recently been introduced, and there are limited data on late-onset IRAEs after several years of initiating treatment. Careful follow-up of cardiac adverse events in long-term treated patients is warranted. Finally, and importantly, treatment with checkpoint inhibitors or sequential therapy with different checkpoint inhibitors, in association with chemotherapy or radiation therapy, is on the rise. Therefore, combination or sequential therapies may contribute to some of the adverse cardiac effects caused by chemotherapy or radiation therapy.

8. Antimetabolites

Fluoropyrimidines, such as 5-fluorouracil (5-FU), *capecitabine*, and *gemcitabine*, are used in the therapies of solid tumors such as gastrointestinal, breast, head, neck, and pancreatic cancer. 5-FU reaches higher levels in cancer cells than in systemic circulation when administered intravenously. One 5-FU pro-drug is capecitabine, which is converted into its active form after oral administration (11, 188, 191, 253, 278, 302).

Adverse effects: Although well-tolerated, both capecitabine and its main compound can induce CTX. The onset of capecitabine CTX is generally rapid. It usually occurs within 4 days from the start of the first cycle of chemotherapy (174, 175). Prospective and retrospective studies have shown that previous events of cardiac ischemia are the strongest risk factors for fluoropyrimidine-induced CTX (195, 309, 310). ECG abnormalities have been found in patients treated with a 24-hour 5-FU infusion in combination with capecitabine. Palpitations and chest pain are the most common clinical manifestations, accompanied by new-onset ECG alterations, such as ST segment deviation, sinus tachycardia, QT prolongation, and signs of myocardial ischemia and acute coronary syndromes. Less frequent are arterial hypertension,

ventricular arrhythmias, LV dysfunction, HF, and cardiogenic shock. Cardiac arrest and sudden death are very rare events, and account for less than 1% of clinical manifestations (5, 198, 309, 408).

The incidence of CTX produced by 5-FU varies between 0-35%, with a mortality rate ranging between 2.2% and 13.3%, depending on the dose, cardiac comorbidities, and route of administration (198, 309, 310). Larger trials and meta-analyses on breast and colorectal cancer patients, however, have reported an incidence of symptomatic CTX of 1.2-4.3% during treatment (205, 407). A recent study found silent ischemia due to cardiac stress test in 6-7% of 5-FU-treated patients (216). Unfortunately, patients without overt CV risk factors are often treated as outpatients. As a result, symptomatic and asymptomatic cardiac events remain undiagnosed because of inadequate cardiac monitoring. This can lead to a discrepancy between observed and actual CTX, in terms of both symptomatic and asymptomatic patients.

Mechanism of adverse effects: Although 5-FU has a brief half-life, active metabolites are retained in all tissues, including cardiac and cancer tissues, resulting in a prolonged exposure of cells to the drug (198, 215, 261). Thymidine phosphorylase, the pivotal enzyme involved in the conversion of capecitabine to 5-FU, is highly expressed in both atherosclerotic plaques and cancer tissues, explaining the higher prevalence of capecitabine-induced CTX in subjects with coronary artery disease. Nevertheless, the pathophysiological mechanisms underlying CTX from antimetabolite drugs remain poorly understood. Several mechanisms have been proposed (Fig. 7): *i*) Reduction in synthesis of nitric oxide (NO), with consequent coronary spasms and endothelium-independent vasoconstriction via the protein kinase pathway (52, 296, 357); *ii*) increased intracellular ROS/RNS, with consequent oxidative stress and cardiomyocyte apoptosis (205); *iii*) increased endothelial thrombogenicity, with consequent induction of acute coronary syndromes (180); *iiii*) interference with DNA and RNA growth by substituting for the normal building blocks of RNA and DNA.

The existence of a synergy between capecitabine and other anti-cancer drugs has also been suggested. Several studies have shown that CTX is more frequent in subjects administered with a combined therapy of capecitabine and either taxanes or lapatinib than in patients treated with capecitabine alone (105, 174, 175, 278). Studies in rabbits have shown that a single high dose of capecitabine caused hemorrhagic infarction of the ventricle walls, proximal spasms of the coronary arteries, and death within a few hours from intravenous injection. In contrast, repeated lower doses produced LV hypertrophy, concentric fibrous thickening of the coronary intima and foci of necrotic myocardial cells (398). Due to the importance of redox stress in antimetabolites-induced CTX, please refer to Sections 10 and 11 for ways to reduce this toxicity.

9. Proteasome inhibitors

Proteasome inhibitors are relatively novel anti-cancer therapies, particularly useful in the therapy of multiple myeloma and other hematologic conditions (amyloidosis, non-Hodgkin lymphoma). The first proteasome inhibitor approved for the treatment of cancer was *bortezomib*; second-generation drugs include *carfilzomib*, *ixazomib*, *delanzomib*, *oprozomib*, and *marizomib* (79, 201, 276).

Adverse effects: Experimental data suggest that chronic (over 12 weeks) proteasome inhibition is associated with systolic dysfunction and increased atherosclerosis (143, 284). A metaanalysis conducted by Xiao and colleagues reported that the incidence of CTX in subjects treated with bortezomib varied with tumor type and treatment regimen, in the range 2.3% to 3.8%, with a mortality rate of 3.0% (427).

Treatment with proteasome inhibitors may be associated with hypertension, HF, myocardial infarction, and cardiac arrest, especially if such therapies are associated with concomitant use of doxorubicin, lenalidomide, and steroids, or in patients with a history of cardiac events (17, 136, 151, 373, 423, 424). The incidence of HF in subjects receiving bortezomib is relatively

low (up to 4%) compared with carfilzomib (up to 25%), a more potent and irreversible proteasomal inhibitor; patients treated with higher doses (≥ 36 mg/m²) of carfilzomib have a higher risk of cardiac toxicity (65, 328, 331).

Mechanisms of adverse effects: Proteasome inhibitors are compounds that block the activity of proteasomes, protein complexes that play a key role in degrading dysfunctional or unneeded proteins; these cellular complexes that break down proteins are particularly important for the functional maintenance of cardiomyocytes. Therefore, cardiac dysfunction may be expected if the function of these complexes is impaired.

Many mechanisms of chemotherapy-induced cardiotoxicity still remain to be clarified. It has been suggested (284) that *bortezomib* alters the function of cardiomyocytes through the impairment of mitochondrial energetics. The cardiomyocytes are contractile cells with a very high demand for ATP and may be particularly sensitive to agents which disrupt mitochondrial activity, such as proteasome inhibitor bortezomib. Furthermore, a reduced synthesis of ATP could trigger the capillary tunneling, as revealed by histopathological examination of heart sections of rats treated with bortezomib (284). Chronic uptake inhibitor of the proteasome is associated with increased oxidative stress at the level of the intima of the epicardial coronary arteries, resulting in thickening of the vessel wall, which can trigger premature atherosclerosis (143).

The addition of other chemotherapeutic agents such as ANT with proteasome inhibitors improves the effectiveness of antineoplastic therapy, however this combination of drugs can cause cardiotoxicity. Spur et al (368) have analyzed the function of the proteasome in primary cardiomyocytes treated with doxorubicin in the presence of proteasome inhibitors. Interestingly, the authors concluded that, opposite to carfilzomib, which targets both the $\beta 5$ standard proteasome and the LMP7 immunoproteasome subunit, immunoproteasome-specific inhibitors with known anti-tumor capabilities for specific cancer cells, such as multiple myeloma, may be advantageous to reduce the mortality of cardiomyocytes, when there is a combination therapy, and therefore may be envisioned as a way to reduce cardiovascular toxicity, when compared to traditional proteasome inhibitors. *Ways to reduce cardiovascular toxicity:* The initial step in CV management of subjects treated

with proteasome inhibitors is to assess their baseline risk for CTX, by taking a clinical history and conducting an examination. More frequent surveillance may be warranted for subjects with higher baseline clinical risk or abnormal cardiac baseline function.

CTX induced by proteasome inhibitors may be reversible in some patients with prompt cessation of these therapies and initiation of traditional HF treatments (123). Angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin II receptor blockers (ARBs) in combination with β blockers are recommended in patients with symptomatic HF similar to the general HF population and in asymptomatic cardiac dysfunction, to prevent further cardiac dysfunction or the development of symptomatic HF in patients at high risk (432).

Single-center experiences have shown a decrease in the occurrence of cardiac events when infusion time of carfilzomib was settled to 30 minutes and a cardioprotective activity of dexrazoxane (17, 136).

In some cases, re-administration of carfilzomib with dose modification is possible. Long-term surveillance should be considered for patients who developed CTX during these therapies and for those in whom cardioprotective treatments have been started, to confirm recovery or to detect irreversible cardiac dysfunction.

10. The importance of mechanisms such as oxidative and nitrosative stress in cardiovascular toxicity: An overview

As reported above, the cardiotoxic mechanisms of several anticancer agents involve an unbalanced generation of ROS and RNS, leading to the so-called *oxidative/nitrosative stress*. ROS/RNS imbalance may derive from increased production or the inactivation of endogenous

antioxidant enzymes by antineoplastic drugs, overwhelming the body's defenses. Moreover, antioxidant resources (especially catalase) are lower in the cardiac tissue compared with other organs (e.g. the liver), making the heart more vulnerable to ROS/RNS injury (257,258). Low physiological levels of ROS/RNS regulate many CV physiological functions (Fig. 8). For instance, H_2O_2 produced by mitochondria is considered an endothelium-derived hyperpolarizing factor and metabolic vasodilator of the coronary circulation (293). High levels of ROS/RNS, overwhelming cellular antioxidant defense systems, may damage biomolecules and dysregulate cellular signaling pathways in the CV system. In particular, ROS/RNS can lead to membrane lipid peroxidation with subsequent membrane damage. ROS/RNS can also lead to DNA damage, and may trigger apoptotic cell death (Fig. 9). Cascade effects would include vacuolization and cardiomyocyte replacement by fibrous tissue, leading to irreversible damage (204, 219, 248-250, 333, 353, 376, 434).

In the CV system, ROS are produced by many mechanisms and enzymes. Among the main ROS producers, there are *xanthine oxidases* and *NAD(P)H oxidases* (NOXs), as well as uncoupled *nitric oxide synthases* (NOSs), *peroxisomes* and *mitochondrial complexes*; ROS production may vary considerably among these enzymes (293, 323, 394). All these ROS producers are affected by multiple anti-cancer drugs (412). The heart is rich in *mitochondria*, which occupy 36-40% of the myocyte volume and produce approximately 90% of the cellular energy. Hence, derangements of mitochondrial function could be particularly critical in cardiomyocytes (293, 294, 394). Cardiomyocyte complexes of the mitochondrial respiratory chain, especially complexes I and III, are the main source of superoxide anions (O_2^-).

A common mechanism of cell death (necrosis and/or apoptosis) involves the opening of the nonselective mPTP, located between the mitochondrial membranes. The opening of mPTPs is facilitated by high ROS levels in the presence of Ca^{2+} overload and cyclophilin D activation. This pore opening allows the free passage of low molecular weight solutes (<1.5 kD), including cytochrome c, into the cytosol, where they can activate the apoptotic process. Moreover, a vicious cycle of ROS-induced ROS release (RIRR) takes place, leading to massive ROS production. If the mPTPs remain open, the mitochondria swell and expand owing to osmotic pressure, and ROS undermine membrane structure via lipid peroxidation; thus these processes disrupt the mitochondrial membrane and favor mitochondria rupture and cell death (293, 294).

Another ROS source strongly affected by antineoplastic agents is represented by the *NAD(P)H oxidase system*, which comprises several isoforms, namely NOXs 1-5 and dual oxidases DUOX1/2. Myocardial NOX2, normally quiescent, produces O_2^- when activated, whereas NOX4, which is constitutively active, generates hydrogen peroxide (H_2O_2). Moreover, superoxide dismutases (SODs) may convert O_2^- to H_2O_2 , which is a relatively stable molecule. In specific compartments, including mitochondria, H_2O_2 may be converted to oxygen and water by catalase and by glutathione peroxidase (GPx). However, especially in the presence of iron complexes, these ROS may be converted to the more toxic hydroxyl radical (OH^-) by several processes within and outside mitochondria (293, 294, 298, 394). Also *peroxisomes*, cytoplasmic organelles specialized for carrying out oxidative reactions, may have a pivotal role in ROS production/regulation in cardiomyocytes. A variety of substrates are broken down by oxidative reactions in peroxisomes, including amino acids, uric acid, and fatty acids. In cardiomyocytes, fatty acid metabolism is very active and peroxisomes are critical for processing long carbon chain fatty acids. Although the role of these organelles in CTX is poorly studied, it is likely they have a key role in determining the fate of cardiomyocytes exposed to cardiotoxic agents (433).

Nitric oxide (NO) is a redox species with both oxidant and antioxidant properties (293, 394). NO responses in tumor biology display a biphasic nature (323). NO is produced by biologically important enzymes, namely the three isoforms of NOS: the endothelial (eNOS or

NOS3) and neuronal (nNOS or NOS1) NOSs, which are constitutively expressed in specific compartments of the cardiomyocytes, and the inducible NOS2 (iNOS), which is induced by pro-inflammatory mediators or by ischemic episodes (293, 394). NO can also be produced by other reactions in biological systems, which are collectively termed 'non-NOS' processes (293, 298, 323). Of note, ROS can react with NO to generate RNS, thus amplifying the production of oxidant compounds, and NOS itself when uncoupled may produce ROS (102, 293, 298, 394). S-nitrosylation (SNO) is the covalent attachment of a NO moiety to a protein thiol group. As recently reviewed (293, 298), SNO is a redox-dependent modification that often exerts an antioxidant effect, shielding critical cysteine residues from oxidation and affecting protein function (Fig. 10).

The toxic effect produced by many anti-cancer drugs is derived from an altered production of ROS/RNS by different cellular components and enzymes (102, 246, 247, 367). For instance, several drugs alter the activity of redox enzymes within and outside the mitochondria, including an impairment of NOSs, respiratory complexes, the Krebs cycle, oxidative phosphorylation, and β -oxidation. This impairment results in oxidative/nitrosative stress, a reduction in antioxidant capacity, and induction of cell death (3, 102, 246, 247, 367). Also iNOS upregulation may be involved in carcinogenesis (140).

In the following paragraphs, we analyze the specificity of *redox alterations* induced by different chemotherapeutics; particular attention is paid to those exerted by ANTs, which for their adverse side effects and for historic reasons are the cardiotoxic agents most studied, and which are still in use for the therapy of solid and hematological malignancies.

The generation of ROS, with a consequent rise in oxidative stress, has been considered a key event in *ANT-induced CTX*. ROS are then effectors of membrane lipid peroxidation, vacuolization, irreversible damage, and myocyte replacement by fibrous tissue (204, 219, 248-250, 333, 353, 376, 434).

ANTs trigger the generation of ROS, affecting the activity of mitochondrial enzyme complexes, NOSs, NAD(P)H oxidases, catalase, and GPx, and leading to oxidative stress and cell injury. ANTs can be quickly converted to unstable metabolites (such as *doxorubicinsemiquinone*), which in turn can react with O₂, producing H₂O₂ and O₂⁻.

2. In addition, ANTs

chelate the free intracellular iron, forming *iron-doxorubicin complexes*. These can react with O₂, leading to the generation of ROS. Finally, ANTs are able to directly interfere with the main iron-transporting and -binding proteins (114, 250). The Ardehali lab (163) has reported that doxorubicin impairs the expression of ABCB8, a mitochondrial iron exporter, with consequent iron accumulation within these organelles and subsequent ROS generation. Accordingly, overexpression of ABCB8 in isolated cardiomyocytes *in vitro*, and in the hearts of transgenic mice *in vivo*, has been proposed as the mechanism protecting from ANT-induced CTX, lowering levels of mitochondrial iron and redox stress. Hearts from patients who developed cardiac dysfunction following ANT treatment exhibit much higher mitochondrial iron levels than normal hearts or hearts affected by different types of dysfunction (163). Such findings support the hypothesis that mitochondrial iron accumulation and oxidative stress play a key role in ANT-induced CTX. Experimental studies have shown that the NRG-1/ErbB axis can modulate and counteract the increase in oxidative stress induced by doxorubicin (262, 390), suggesting that CTX from ErbB2 blockade can also involve a dysregulation of redox homeostasis (250).

A portion of cardiac damage induced by ANTs results from their high affinity for *cardiolipin*, a mitochondrial membrane phospholipid involved in apoptotic pathways. The interaction of ANTs with cardiolipin leads to a high concentration of the drug in these organelles. Once accumulated in the mitochondria, the drug may exert adverse effects such as ROS generation, inhibition of oxidative phosphorylation, and mitochondrial DNA damage. During the initial phases, ROS can lead to peroxidation of cardiolipin, which may induce the release of

mitochondrial apoptogenic factors, including cytochrome c, which in turn can trigger more cardiolipin peroxidation. This leads to a cycle that exacerbates ANT-induced injury. Of note, NO may inhibit the peroxidase activity of cytochrome c on the cardiolipin complex and can thereby block cardiolipin oxidation. Thus, it may be argued that site-specific and appropriate amounts of NO, which exerts antioxidant properties, may counteract the toxic effects of ANTs (121, 308, 413).

Although much of ROS generation appears to take place in the mitochondria, soluble oxidoreductases of the cytoplasm, such as the xanthine oxidase and coenzyme of the NAD(P)H-dependent cytochrome P450 reductases of the ER, may be targeted by ANTs in altering redox equilibrium. For example, doxorubicin deoxyglycone may be obtained by a reduction process occurring in the ER. Deoxyglycone may then accumulate in the membranes, where it can alter the function of complex I (NADH dehydrogenase) in membrane mitochondria, or the NOXs, in the plasma membrane (389). Both an excessive production of NO by ANT-induced iNOS and a reduced level of NO, resulting either from the quenching of NO by the superoxide anion to form peroxynitrite (ONOO⁻) or from uncoupled NOS, have been described as responsible for some of the damage induced by these drugs (103). More studies are required to elucidate the role of such enzymes and of other less characterized intracellular signaling molecules in ANT-induced CTX. However, these data confirm how the oxidative reactions at the basis of ANT-induced cardiac dysfunction are involved in most kinds of HF, suggesting that timely innovative pharmacological strategies that interfere with specific molecules involved in heart dysfunction, such as p53, may represent a potential common approach in the fight against HF (250).

Oxidative stress may also play a role in CTX derived from *TKIs*: It has been observed that direct infusion of *sunitinib* in different experimental preparations provoked a dose-dependent cardiodepressant effect, accompanied by decreased levels of intracellular Ca²⁺, with a concomitant rise in ROS generation (314).

In addition, *5-FU* can also induce oxidative stress in cardiomyocytes and endothelial cells. In particular, the toxic effect exerted by this drug on the vascular endothelium determines eNOS dysregulation, endothelin 1 upregulation, and the activation of protein kinase C. These effects may lead to endothelium-dependent and -independent vasoconstriction, and subsequently to coronary spasms (5, 365).

10.1 Drugs with antioxidant properties

The cardiotoxic mechanisms involving oxidative stress provide the rationale for using drugs with antioxidant properties (29, 34, 73, 219, 224, 242, 350, 366, 379, 381), (Fig. 11).

The iron-chelating drug *dexrazoxane* has been identified as the most promising cardioprotective strategy in the past years and, up to now, is the only cardioprotective drug approved by the FDA for ANT-induced CTX. Dexrazoxane is a pro-drug that, once it enters the cardiomyocyte and rapidly turned into its active form, counteracts the formation of ANT-iron complexes and the subsequent formation of ROS (358) (Table 2). Its efficacy has been extensively tested in multiple randomized trials and two pooled analyses (350, 379), and confirmed in different subsets of cancer patients (222, 381).

It is likely that dexrazoxane possesses unique pharmacodynamic protective mechanisms, because no other iron chelator has shown any cardioprotective effects (358). At the molecular level, dexrazoxane has been shown to modify the Top2 β configuration, preventing its interface with ANTs, thereby impeding the realization of the Top2-DNA cleavage complexes (213, 229). However, dexrazoxane has been underused in recent years, despite strong evidence of its cardioprotection (367). While CTX mitigation induced by new-generation β blockers could be due more to their antioxidant properties than to their β -adrenergic receptor blocking action (243, 366, 430), it appears that the cardioprotective effect of iron chelators does not stem from their antioxidant properties, but rather from their ability to affect iron regulatory proteins and to reduce iron accumulation (42, 114). Interestingly, close derivatives of

dexrazoxane lacking Top2 β were found not to be protective in relevant chronic ANT CTX models (178, 242) which also suggest Top2 β importance in the cardioprotective mechanism. These observations indicate that anthracycline-mediated damage relies on complicated alterations of the intracellular metabolic pathways or Top2 β interaction. Moreover, recent preliminary data from Stěrba and coworkers suggest that cardioprotective effects of dexrazoxane against chronic anthracycline cardiotoxicity are due to its interaction with Top2- β , rather than to its metal chelating metabolite (213, 372). Nevertheless, the discordant results underline the need for further investigation to ascertain the exact biological interaction of anti-cancer drugs with the cellular redox balance.

10.1.1 β blockers: Anti-adrenergic and antioxidant drugs

β blockers are a cornerstone therapy in patients with reduced LVEF to prevent symptomatic HF (311), and many researchers encourage their use in asymptomatic ANT-related LV dysfunction (62, 367). The rationale for β blocker use in ANT-induced CTX rests mostly on experimental indications of their cardioprotective effects. Moreover, a recent retrospective survey in breast cancer patients administered with ANTs and trastuzumab showed that patients who received β blockers during their treatment exhibited a significantly lower incidence of HF, supporting the hypothesis that blockage of the β -adrenergic receptor (β -AR) may be cardioprotective during antineoplastic therapies (347) (Table 2; Fig. 11).

Long-dated evidence shows β -AR signaling alterations in ANT-induced cardiomyopathy-like features and in other forms of dilated cardiomyopathies (108) and several animal models have shown a specific positive effect of β -AR blockage in mitigating oxidative stress, reducing myocardial calcium overload (14, 275), and preserving epidermal growth factor signaling (87, 189).

The cardioprotective role of the new-generation β blockers, like carvedilol and nebivolol, has also been evaluated. In one study, carvedilol, a non-selective β - and α 1-AR antagonist with strong antioxidant properties, was compared to atenolol, a β blocker without antioxidant properties, and showed greater protection against ANT-induced cardiomyopathy; the protective effect of carvedilol, therefore, seems to be related more to its antioxidant properties than to the β -AR blocking action (243). Carvedilol can prevent ANT-induced ROS release, cardiomyocyte apoptosis (366), and mitochondrial respiration alterations, along with calcium overloading (337). A small randomized placebo-controlled clinical trial on the cardioprotective effect of prophylactic-use carvedilol in patients undergoing ANT chemotherapy showed a reduced incidence of LV systolic and diastolic dysfunction in the carvedilol group (181). However, strong clinical evidence of the cardioprotective effect of carvedilol is still lacking.

Nebivolol is a cardio-selective β blocker with limited vasodilating properties related to its interaction with the L-arginine/NO pathway. In an experimental model of ANT-induced CTX, treatment with nebivolol, and to a lesser extent with carvedilol, led to an improvement in LV function associated with increased NO levels and a significant reduction in oxidative stress (71, 393, 394). A small randomized placebo-controlled study on the prophylactic use of nebivolol in patients undergoing ANT chemotherapy showed, at the 6-month follow-up, a reduced incidence of LV dilatation and systolic dysfunction in the nebivolol group compared with the placebo group (183). In addition, by enhancing prosurvival ERK signaling after ErbB2 inhibition (87), β blockers can also prevent trastuzumab-related CTX (Table 3); β blockers are now studied in a series of clinical trials such as the MANTICORE 101 and the SAFE trials (33). As said, recent data from the PRADA trial indicated that the β 1 blocker metoprolol was not cardioprotective (128), thus supporting the use of unbiased β 1 and β 2 blockers (382).

In summary, different β blockers are not similarly effective in treating CTX. The molecular and cellular mechanisms by which β blockers may confer cardioprotection are not completely clear. To date, a cardioprotective treatment with β blockers should still demonstrate its efficacy in large clinical trials. Additionally, in clinical practice, use of β blockers is hampered by

their side effects in an already-fragile patient, suggesting their use only in patients with a high CTX risk.

10.1.2 The redox role of renin-angiotensin-aldosterone system (RAAS) antagonists:

angiotensin-converting-enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers

(ARBs) Many studies have found a key role for RAAS in modulating ANT-induced CTX (13). ACEIs and ARBs have already been shown to exert positive effects in reducing the progression of LV dysfunction and preventing HF in asymptomatic high-risk patients (311).

The rationale for using RAAS blockade drugs in this setting is based on the high risk of developing myocardial dysfunction after ANT treatment. Experimental studies have shown the efficacy of ACE-Is in countering ANT-induced CTX, both acute high dose (1) and single low dose (24). The underlying mechanisms of their positive effect against ANT-related CTX contribute to neutralizing ROS damage, reducing interstitial fibrosis, avoiding intracellular calcium overload, and improving mitochondrial respiration and cardiomyocyte metabolism (1, 24) (Table 2; Fig. 11). Indeed, activation of the AT1R produces direct adverse cardiovascular effects by stimulating NADPH oxidase, which is involved in the genesis of oxidative stress, and initiating MAPK, related to cell growth, inflammation, hypertrophy, and apoptosis (25).

Experimental animal models of acute and chronic *ANT-induced cardiomyopathy* showed a cardioprotective role for prophylactic administration of enalapril, captopril, and lisinopril (1).

In a study of 115 patients treated with ANTs, enalapril was shown to significantly reduce the incidence of LV dysfunction in comparison with a placebo (36).

Candesartan has been shown to treat experimental cardiotoxicity already induced by anthracyclines (364); while pre and post treatment with telmisartan protected against acute doxorubicin-induced cardiotoxicity in rats (164). Telmisartan is the only ARB modulating peroxisome proliferator-activated receptor- γ (PPAR- γ), and, therefore, affecting the bioavailability of NO, and inhibiting inflammatory molecules such as interleukin 6 (IL-6) and tumor necrosis factor (TNF) (428). In a small prospective study, telmisartan was shown to mitigate subclinical cardiotoxic effects (changes in strain rate) of epirubicin, with IL-6 and ROS increasing significantly in the placebo arm but not in the telmisartan arm (34). Telmisartan could reverse acute (early) EPI-induced myocardial dysfunction and maintain a normal systolic function up to the 18-month follow-up (73, 74). IL-6 and ROS increased significantly in the placebo arm but did not change in the telmisartan arm. In another study, valsartan showed a cardioprotective effect on acute cardiotoxicity in patients treated with high doses of ANTs (274).

Recent clinical trials have shown that a combination of ACE-Is and β blockers is beneficial in treating ANT-induced CTX (23). Many other ongoing clinical trials are evaluating the role of ACE-Is and ARBs as cardiopreventive agents that may act by decreasing angiotensin-induced blockade of the neuregulin 1/ErbB pathway.

Finally, a recent meta-analysis showed that the prophylactic administration of ACE-Is and ARBs in patients on ANT therapy was associated with a reduced relative risk of developing CTX compared with patients on a placebo (180). To date, however, a cardioprotective treatment with ACE-Is or ARBs still requires a demonstration of efficacy in large clinical trials.

Additionally, in patients with anti-angiogenic drug-induced hypertension, nondihydropyridine calcium channel blockers are not indicated, because of the pharmacokinetic interaction of sorafenib and sunitinib with CYP3A4 (33, 236). Thus, acknowledging the other mechanisms responsible for sunitinib-induced CTX, i.e., disrupted mitochondrial function and impaired myocyte energy homeostasis, ACE-Is and β blockers (85, 106) could form an effective cardioprotective strategy (Table 3). Unfortunately, no clinical study to date has shown a role for these drugs in preventing sunitinib-induced CTX (33).

10.2 Novel strategies in cardioprotection against ANT-induced CTX

Several CV drugs have tested as potentially effective in counteracting ANT-induced CTX, and particularly *statins*, *ranolazine*, and *phosphodiesterase-5 inhibitors*.

Lovastatin and fluvastatin, HMG-CoA reductase inhibitors, showed a cardioprotective effect in experimental studies (159, 320). Of notice, these data derive from acute, subacute experimental cardiotoxicity studies and cell-based studies performed on proliferating H9c2 cell line, not cardiomyocytes. Therefore, effects of anthracyclines in this setting deserve caution since these drugs possess strong antiproliferative action besides cardiotoxic effects. The effects of the statins on the Top2b have not been directly demonstrated in the studies, just indirectly suggested to be Top2b-related. Beside these caveats, left ventricular systolic dysfunction induced by doxorubicin was not affected by lovastatin (142). Only small clinical studies have evaluated the effects of statins in patients treated with ANTs (48, 348), reporting only minor positive results. Unfortunately, the study from the Marwick group (348) was a retrospective observational analysis, and even Chotenimitkhun and collaborators (48) do not appear to have conducted a standard controlled randomized trial. Therefore, larger studies are therefore required to confirm these findings.

Late I_{Na} inhibition with ranolazine has been proposed as a cardioprotective strategy in several experimental models of cardiac dysfunction (316, 391, 394). Ranolazine was shown to preserve heart function in mice treated with ANTs by reducing oxidative stress. Inhibiting elevated $[Na^+]_i$ levels with ranolazine would prevent calcium overload and the occurrence of oxidative damage by suppressing ROS generation, offering an advantage over conventional antioxidant strategies that counteract ROS after their production (196). The INTERACT study (259), designed to assess whether ranolazine could prevent ANT-induced diastolic dysfunction, indicated that ranolazine was a promising cardio-oncologic drug, but more convincing data are still required.

Phosphodiesterase-5 inhibitors have also been tested as cardioprotective agents. Sildenafil demonstrated cardioprotective activity against ANT-induced LV dysfunction by opening mitochondrial

K_{ATP} channels, preserving mitochondrial membrane potential and myofibrillar integrity, and preventing cardiomyocyte apoptosis (100). *Tadalafil* attenuated ANT-induced cardiomyopathy through NO-mediated increases in cGMP levels (177, 197).

Finally, redox mechanisms have also been proposed for the ability of NRG-1 to limit antineoplastic drugs-induced damage in adult rat cardiomyocytes (390).

Another redox compound attracting the interest of researchers and cardio-oncologists is *hydrogen sulfide* (H_2S), whose role in cancer is still poorly understood. The discoveries that ROS-induced inhibition of cystathionine gamma-lyase, a key enzyme in the synthesis of H_2S , is involved in ANT-induced CTX in H9c2 cardiomyocytes, and that the administration of exogenous H_2S can confer protection against this CTX, have suggested a new tool with antioxidant properties in therapeutic strategies against antineoplastic drugs-induced CTX (33, 247, 295). Further research in appropriate animal models is required, as well as multi-centric randomized trials that compare the efficacy of these new compounds with that of already approved cardioprotective drugs.

Experimental studies have shown that sunitinib inhibits AMPK activity, while restoration of this enzyme's activity inhibits cell death (186). It has been speculated that promoting AMPK activity with *metformin* may reduce sunitinib-induced CTX. Although metformin can counteract dysfunction in different experimental models of cardiac injury (53, 129) (Table 3), an *in vitro* study that focused on sunitinib-related CTX did not find any beneficial effect of metformin (33). As mentioned above, a recent study (98) demonstrated that TrkB, a tyrosine kinase receptor, and its endogenous ligand BDNF could directly modulate the cardiac excitation-contraction coupling, independently or in parallel with GPCR-mediated signaling, supporting the concept that inhibition of the tyrosine kinase receptor with antineoplastic drugs can interfere with fundamental pathways, damaging cardiac contractility (106). At the same time, this study highlights BDNF as an alternative potential therapeutic strategy for HF.

10.3 Non-pharmacologic strategies

Apart from pharmacologic interventions, we should also consider that *nutritional supplementation and exercise training* may have important antioxidant properties (8, 139, 192, 345, 346, 359, 369).

Dietary supplementation of antioxidants showed to be able to alleviate doxorubicin cardiotoxicity in animal models (8, 426). Although there is still scant evidence in both quality and sample size, suggesting that some antioxidant supplementations may lower ANT-induced CTX (109). Non-pharmacologic strategies for countering ANT-induced CTX include lifestyle interventions and exercise “prehabilitation,” a type of preventive exercise rehabilitation. It has been speculated that aerobic exercise can decrease ROS generation, inhibiting pro-apoptotic signaling, restoring proper calcium cycling, and stimulating the AMPK pathway, thus improving myocardial energetics (345) (Table 3). In addition, exercise can have a positive impact on CV risk factors, such as hypertension, high cholesterol and lipids, overweight and obesity, and high blood glucose or diabetes (192). In cancer survivors, a short period of mixed aerobic and resistance exercise builds tolerance and flexibility in physical activity (369). Although several studies have shown a role for aerobic exercise in countering ANT- (343) and trastuzumab- (139) related CTX, additional work is needed to better characterize the effects of training on antineoplastic drug-induced CTX (346).

10.4 Biomarkers of oxidative/nitrosative CTX

Since the importance of ROS/RNS production as early mediators of chemotherapy-related CTX has been ascertained, we should identify useful circulating *biomarkers of oxidative/nitrosative CTX*. Biomarkers with redox significance include the metabolomic identification of acetate and succinate (8). A decrease in NAD(P)H:quinone oxidoreductase 1 activity and an increase in ROS generation by NAD(P)H oxidases have been considered early biomarkers of ANT-induced CTX (283). A significant variation in IL-6, IL-6R, and ROS has been observed together with a change in the enzymatic activity of GPx, which was correlated with an early variation in longitudinal systolic function in patients after the administration of epirubicin (73, 74).

Other potential CTX markers with redox importance under investigation in cardiology are high-sensitivity C-reactive protein, heart-type fatty acid-binding protein (H-FABP), glycogen phosphorylase BB (GPBB), and circulating microRNAs, especially microRNA-146a (miR-146a). These are considered new potential markers for the diagnosis and risk stratification of acute coronary syndromes, and may be helpful in early detection of anti-cancer CTX however, the clinical data available in the chemotherapy-induced CTX scenario remain insufficient (131, 152-155, 371, 419). For discussion on other biomarkers see sub-section 11.4.

1. Early detection, monitoring, and management of heart and vascular toxicities

11.1 Cardioncology: an expanding science for an expanding problem

Assessing CTX from antineoplastic drugs is essential. Screening for CTX at a pre-clinical stage is essential when investigating the effects of TKIs. Many of these drugs cause an increased risk of arrhythmia, thus most of the pre-clinical work focuses on hERG (K⁺ channel). A major limitation of *in vitro* work is that primary myocyte cultures of animal or human hearts dedifferentiate and die after a short while. Hence, assays based on stem cells and on the use of engineered heart tissue may better reflect *in vivo* settings. Such experimental studies could integrate assessment of several effects, including those on membrane action potential, calcium cycling, and myofilament function, as well as those on gene expression and cell survival (69, 88, 236, 376).

In clinical practice, most of the methods used to assess heart function are often inaccurate, and may also mislead physicians to stop potentially lifesaving therapies. Of note, patients with advanced cancer may already exhibit potential confounder symptoms mimicking anticancer drugs' side effects. Moreover, complications such as myocardial ischemia, arterial

hypertension, and dysrhythmias are readily recognized, but identifying mild LV dysfunction (especially at a subclinical stage) can be more challenging (376). In this context, a prompt and sensitive monitoring of CV function plays a pivotal role.

In addition, the time point when CTX can become clinically overt varies substantially. Several antineoplastic drugs, (i.e. ANTs) can induce progressive cardiac remodeling and late *cardiomyopathy*, while others (i.e. trastuzumab) can produce transient LV dysfunction without known long-term consequences (376, 432). Furthermore, the inability to exactly predict the long-term consequences of tumors, leads to false diagnosis of CV complications. Owing to all these concerns, cardioncology, a new branch of CV sciences recently developed, with the aim to prevent, identify and treat CV complications of cancer therapy, optimizing clinical status for cardiac patients who need potentially cardiotoxic treatment, facilitate in any way cancer therapy in patients with CV complications and surveille for late side effect in cancer survivors.

11.2 Diagnostic tools for CTX detection

The most common clinical diagnostic tools for screening and detection of CTX are biomarkers and cardiac imaging including echocardiography, multiple-gated acquisition (MUGA) scan and CMR (Table 4). Nevertheless, an ECG is recommended for all subjects before and during therapies, particularly for detecting arrhythmias and QT interval prolongation. Moreover, subjects on pyrimidine analogs should be monitored closely for cardiac ischemia by regular ECGs, and chemotherapeutic treatments should be withheld if ischemia is observed (432).

11.3 LVEF and emerging modalities for assessing myocardial damage: some claryfing points

LVEF is the most frequently used parameter for assessing myocardial function, and echocardiography and MUGA scans are largely employed in clinical practice for this purpose (40, 41, 62, 171, 206, 234, 299, 307, 376, 432, 438). An LVEF decrease (>10%) to a value <50% identifies patients with CTX in both imaging modalities (307, 432). Compared with echocardiography, MUGA provides the advantage of a high reproducibility, but is hampered by significant disadvantages, such as cumulative radiation exposure and no data on other cardiac structures (299, 432). However, the choice of modalities for an early detection and monitoring of CTX depends upon local expertise and availability being careful to use the same imaging modality with the best reproducibility for continued screening throughout the treatment period (432). Imaging techniques that provide additional relevant clinical information (e.g. right ventricular function, pulmonary pressures, valvular function, pericardial evaluation) and high-quality radiation-free imaging are preferred (307, 432). Confirming LVEF decrease by repeated cardiac imaging (preferably by echocardiography) 2 to 3 weeks following the baseline initial decrease in LVEF is strongly recommended, as well as categorizing LVEF reduction as asymptomatic or symptomatic, and repeating echocardiography measurements during follow-up (432). Repeated MUGA is not recommended as a first-line option, and should only be conducted if the radiation exposure is less than 5 mSv (432).

On the other hand, echocardiographic measurements, though simple, non invasive and readily available, are often variable and of low sensitivity (290), because of the serious damage and myocyte loss leading to an observable reduction in LVEF (92, 416). On these grounds, novel indices of ventricular function are being introduced (37, 146, 150, 206, 386). Speckle tracking echocardiography has shown the highest sensitivity in detecting early alterations in LV function associated with future development of *cardiomyopathy* (134, 146, 306, 307, 395, 438). In particular, a global longitudinal strain (GLS) >15% relative percentage reduction from baseline can identify patients at risk for CTX (97, 172, 307, 432).

Other imaging modalities, such as CMR, appear very promising, although their availability is still limited (97, 238, 290, 299, 388, 415). CMR is the gold-standard technique for LVEF estimation and can identify myocardial edema, inflammation, capillary leak, and fibrosis,

enabling an accurate diagnosis of early and late CTX (239, 388, 432). Other recent strategies include measuring uptake of iodine-124-metaiodobenzylguanidine (MIBG), a radiolabeled analog of norepinephrine, which is reduced after myocardial insults (145, 239, 415). In addition, antimyosin antibodies that detect myosin exposed after cardiac damage could be useful (235, 239, 401, 402), while the uptake of radiolabeled chemotherapeutics could be used as a predictor of CTX (18, 239, 301).

11.4 Cardiac biomarkers. Troponins and natriuretic peptides can be correlated with findings from cardiac imaging for early detection of CTX (283, 292). Natriuretic peptide level elevations were demonstrated to predict the development of future CTX in patients with NHL and with breast cancer (99, 119). Persistent B-type natriuretic peptide (BNP) rises, after exposure to anthracyclines, were more predictive of following LV dysfunction than transient elevations (327, 335). However, the utility of NPs for predicting anticancer drugs-induced CTX is still controversial. Indeed, several studies did not confirm a prognostic value for BNP levels especially when this biomarker was used alone (66, 340, 378). It has been observed that troponins I and T can predict late ANT-induced CTX in children (223) and in adult patients undergoing high dose chemotherapy. Not only the increase, but also the pattern of the elevation and particularly a persistent increase after 1 month since treatment, added prognostic information. Conversely persistently negative TnI identified low risk patients who did not need a strict cardiological follow up (38). Patients with troponin increase may benefit from early cardioprotective treatment with ACE-Is (36). In patients treated with trastuzumab, especially after previous exposure to ANTs, troponin I elevation can identify those who will develop LV dysfunction and who will not recover in spite of treatments for HF (37). High-sensitivity troponin I is more sensitive in the evaluation of subclinical depletion of cardiac physiologic reserve and a new elevation of this marker predicted subsequent LV dysfunction in patients receiving conventional dose of ANTs and/or trastuzumab (203). The combination of high-sensitivity troponin with GLS predicted the risk to develop future cardiotoxicity with increased sensitivity (93%) and negative predictive value (91%) compared with the evaluation of a single parameter in patients with breast cancer (340). Therefore “cardiac biomarkers plus cardiac imaging” should be encouraged to early detect CTX. There is still scant data supporting the use of biomarkers to predict future cardiac dysfunction due to immune and targeted cancer therapies. Few data indicated an increase of troponin in subjects administered with sunitinib and sorafenib for metastatic renal cell carcinoma, who developed ventricular function impairment (344). Several other biomarkers have been studied or are under investigation to stratify the risk of cardiotoxicity. Myeloperoxidase (MPO), an index of oxidative stress, measured after anthracycline administration, seems to correlate with subsequent development of CTX (203). Fatty acid binding protein (FABP) and Glycogen phosphorylase BB (GPBB) have also been proposed as novel biomarkers of chemotherapy mediated cardiac damage even more precocious of troponin and BNP (86, 152, 153). MicroRNAs have emerged as an attractive tool to detect myocardial injury. miR-146a may induce downregulation of ErbB4 and subsequent stimulation of apoptotic pathways. Preclinical studies have shown increased levels of miR-146a after doxorubicin administration (155). However more trials with long-term follow-up are needed to validate these data.

The use of cardiac biomarkers in the prediction of cardiotoxicity has several advantages (accuracy, reproducibility, high-sensitivity, wide availability and relatively low cost), but also limitations, for example inter assay variations, insufficient evidence to establish specific cut offs for enzyme elevations in this setting, uncertainty in the timing of blood sampling (432). Standardization in the assessment of cardiac toxicity using biomarkers is needed and multicentre trials are strongly required before establishing more clear recommendation (376) Table 5 summarizes main biomarkers evaluated for the detection of cardiac toxicity.

11.5 Detection of vascular complications: old and new strategies

Structural endothelial damage, endothelial dysfunction, acceleration of atherosclerosis,

prothrombotic actions, and vascular inflammation are some of the underlying mechanisms of cancer therapy-related changes in vessel function. *VEGF inhibitors*, TKIs (such as nilotinib, ponatinib, dasatinib), cisplatin, 5-FU and ANTs can induce hypertension, ischemia and thromboembolism (TE) through their endothelial toxicity. Coronary artery disease, (CAD), stroke, peripheral artery disease (PAD), pulmonary arterial hypertension (PAH), arterial/venous TE disease and nephrotoxicity are the main clinical presentations of vascular damage by cancer therapy. In particular, nuclear cellular actions by ANTs may adversely modulate collagen turnover and vascular wall homeostasis, leading to acute damage (endothelial dysfunction, increase in smooth muscle tone) and chronic damage (atherosclerosis, increased collagen synthesis), and resulting in an impaired CV coupling (81, 84, 273). Age and CV risk factors may influence the extent of cardiac dysfunction (Fig. 12). *VEGF inhibitors* increase vascular tone due to a decrease in NO production, increased peripheral resistance from endothelial damage (sloughing) and dysfunction, and capillary rarefaction (96). *Cisplatin* can induce myocardial ischemia through an increased procoagulant status.

For an early detection of vascular complications, current recommendations (432) simply suggest to monitor CV risk factors, assess patient functional status, measure blood pressure before cancer treatment and optimize antihypertensive therapy during treatment with a goal of < 140/90 mmHg (particularly in patients treated with *VEGF inhibitors*). Moreover, the identification of patients with pre-existing CAD in those undergoing 5-FU is of paramount importance since this drug substantially increases the risk of developing myocardial ischemia with a vasospasm recognized mechanism. In addition, it should be considered that clinical factors (cancer-, treatment- and patient-related) could be related to enhanced risk of venous thromboembolism in subjects administered with TKIs. *Nilotinib*, *ponatinib*, and BCR-ABL TKIs used in treating CML are, instead, associated with PAD and stroke. The evaluation of PAD risk at baseline (risk factor assessment, clinical examination, ankle-brachial index measurement) is therefore recommended in these patients (432). Moreover, cerebrovascular ultrasound screening is indicated in subjects irradiated for head and neck cancer or lymphoma, especially beyond 5 years after irradiation (432).

However, a common standard approach useful in clinical practice for an early detection of vascular complications such as atherosclerosis is missing, to date.

The assessment of arterial stiffness, which early increases in atherosclerotic process, in order to provide vasculotoxic profiles of chemotherapeutic agents seems to be very promising. These could be useful in the future in improving therapeutic strategies (84, 179, 273, 425). Drafts et al. found, by magnetic resonance imaging of the aorta, an early (approximately 3 months) and abrupt increase of pulse wave velocity (PWV), a marker of arterial stiffness, which was dose-, age-, and CV risk factor-independent in patients treated with ANTs; furthermore, this increase was accompanied by a subclinical reduction in LVEF and strain (81). This is one of the first demonstration of early atherosclerosis with associated impaired ventricular-arterial coupling in cancer survivors. More recently, a marked stiffening of large elastic arteries was demonstrated by applanation tonometry also in patients undergoing VEGF-inhibitors (265). Accordingly, ACE-Is should be preferred because of their antistiffening properties in the aorta in hypertensive patients treated with ANTs and VEGF inhibitors.

11.6 Timing of clinical evaluation and follow-up: the importance of risk factors assessment

To date, no algorithm has been established for evaluation and follow-up of patients before, during, and after cancer therapies. However, a strong collaboration between *cardiologists* and *oncologists* is required to monitor and treat oncology patients (3, 432). Of course, the cardiooncology team must be equipped appropriately to address the most common questions (i.e. CTX prediction, prevention strategies, high-risk patient monitoring, management strategies) with an evidence-based approach (410, 425).

Long-term surveillance of cancer survivors with a potential for late-onset CV complications should involve cardio-oncology teams. According to recent clinical guidelines on cancer treatment and CV toxicity, the first step in cardioprotection should be the identification of subjects at higher risk; this depends on several factors: cumulative dose, body mass index (BMI) >30 (especially for anti-HER2 compounds), age (elderly and pediatric population treated with ANTs) (199, 376, 380), concomitant or previous radiation therapy, previous cardiotoxic cancer treatment, pre-existing conditions such as CVD, demographic and other CV risk factors, and lifestyle and genetic risk factors that may predispose patients to CTX at lower ANT doses (37, 50, 432). Although recent experimental studies from Moulin and collaborators (271) seem to suggest the opposite, female patients appear to be more susceptible to doxorubicin damage (222-224).

Gender-specific pharmacokinetic differences or even a degree of protection conferred by androgens could be responsible for this phenomenon. It has been observed that testosterone can reduce ANT-induced damage in cardiac myocytes *in vitro* (6).

11.7 Drug-specific timing for CTX monitoring and treatment

The exact timing and frequency of imaging and/or biomarker sampling will depend on the specific antineoplastic therapy, total cumulative dose, treatment protocol and duration, and baseline CV risk (432).

ANTs: Doxorubicin and epirubicin can induce acute CTX (including ECG changes, supraventricular and ventricular arrhythmias, or transient LV dysfunction), which is usually reversible, develops in <1% of patients immediately after infusion of ANTs; early or subacute cardiotoxic effects, occurring within the first year of treatment, and late effects with typically are those manifesting after a median of 7 years. Early or subacute CTX, the most frequent, requires a baseline evaluation and further assessment at the end of the treatment, particularly in presence of an enhanced risk for CTX, or with consecutive treatment with potentially cardiotoxic-targeted therapeutics. For higher dose anthracycline-containing regimens, and in subjects with high baseline risk, earlier evaluation of heart function after a cumulative total doxorubicin (or equivalent) of 240 mg/m² should be considered (432).

Anti ErbB2: Since patients receiving anti-ErbB2 therapeutics frequently receive also ANTs, a baseline evaluation is always recommended. Usually, cardiac assessment is performed every 3 months during and once after completion of anti-ErbB2 therapies. An improvement in early detection of cardiac dysfunction with troponins and GLS measurements every 3 months during adjuvant trastuzumab treatment has been demonstrated. Troponin dosage with every cycle may be considered in patients with high baseline risk (variability in the timing of trastuzumab induced cardiac dysfunction) (432).

VEGF-inhibitors: The best timing of surveillance strategies still needs to be clarified. There is high variability in the time of occurrence (early after treatment and delayed for several months). Currently it is reasonable to consider evaluations every 6 months initially until stability in values of LVEF is achieved. With high baseline risk, it is better to perform early clinical assessment in the first 2-4 weeks after starting targeted therapies. There is limited evidence to support any specific surveillance strategy. In addition, treatments with anti VEGF-inhibitors (236) pose a high risk (11-45%) of inducing new hypertension or destabilizing previously controlled hypertension, including severe hypertension in 2-20% of cases (255, 432). Monitoring blood pressure is therefore essential, and susceptible patients should preferably be treated with ACE-Is, ARBs, or β blockers instead, considering the beneficial role of these drugs in HF (236, 370, 376).

With regards to therapeutic implications, beyond antihypertensive treatment, eventual standard HF therapy can be administered (62, 376, 392), and with good life expectancy, aggressive treatments with LV-assist-devices can also be considered (322, 376). To prevent and treat vascular complications, such as PAD, antiplatelet therapy is recommended (432). Significant stenosis (e.g. those of carotid arteries) may need stenting or surgery. Targeted therapy for

PAH can be used temporarily or permanently. Management of QT prolongation is usually dependent on correction of the predisposing factors (e.g. concomitant electrolyte abnormalities, QT-prolonging drugs). Commonly, an individualized approach for the management of atrial fibrillation is needed, and decisions on rate or rhythm control should be patient-centred and symptom directed. Anticoagulation for venous TE prevention in patients with cancer should always be considered according to the patient's bleeding risk and life expectancy (432).

12. Conclusions and perspectives

Antineoplastic therapies have led to a prolonged life expectancy for many patients, but CTX is a relatively common adverse effect of these therapies. Apart from direct myocardial toxicity of single drugs, cardiac dysfunction and HF may be exacerbated by drug-drug interactions, which are not only due to treatment with multiple anti-cancer drugs, but also to the disparate drugs necessary to mitigate symptoms. Even targeted therapies that were traditionally considered less toxic may exert CTX. Moreover, drugs used to prevent cardiovascular complications have raised some concern about cancer induction (68). Improving the quality of patient care in the CTX setting is, indeed, a complex issue. Despite several proposed strategies to reduce anticancer drugs-induced CTX, LV systolic dysfunction and HF still occur in cancer survivors. The scientific community has recognized the complexity of these toxicities, and is developing multidisciplinary strategies to prevent or minimize CTX and its long-term effects (425). Understanding the mechanisms by which anti-cancer treatments affect the heart is critical for implementing optimal drug design and proposing alternative therapies. Multidisciplinary teams should work to develop methods to reduce the influence of risk factors and to detect and treat potential CTX (3). Early detection requires awareness of chemotherapy-related cardiac dysfunction, as well as appropriate prevention, cardiac evaluation, and follow-up. These aspects are needed to protect individuals predisposed to CVD. Very often, many of the patients developing adverse CV events have preexisting known CVD or at least CV risk factors, for which they should receive appropriate treatment and adequate prevention counseling. Measures "*that rest on common sense,*" such as exercise, are recommended for all patients receiving potentially cardiotoxic therapy (367). These measures include the management of preexisting comorbidities and recommendations for a healthy lifestyle, and should be suggested both before and after initiating cancer therapy. In the absence of specific cardiac monitoring guidelines for potentially cardiotoxic agents, the evaluation and monitoring of LVEF must be considered. However, the prognostic value of serial measurements of LVEF during treatment to detect and monitor CTX remains controversial. Several biomarkers have been proposed, which ideally should be simple to measure, widely available, low-cost, and extensively used in treating other pathological conditions. For instance, troponin has been proposed for CTX monitoring, but its practical use has yet to be shown definitively (292, 376, 432). Hope for progress comes from the development of new promising technologies, including the *omics sciences*, immunotherapy, investigations of ROS-dependent pathways, and further work involving stem and progenitor cells (250) from both adult and embryonic sources, which so far have been investigated for their capacity to repair and regenerate CV tissues (233, 260). Since actively replicating cells are the main target of anti-cancer chemotherapy, stem and progenitor cells may be targeted by drugs involved in the onset and development of chemotherapy-induced CTX (20, 260, 363). Specifically, cardiac-derived progenitor or stem cells (CPCs/CSCs) from the adult heart have recently attracted attention as a tool for studying chemotherapy-induced *cardiomyopathy* and HF (67, 72). CPCs/CSCs which may exist in specific architectural microenvironments known as "cardiac stem cell niches", have very recently entered the clinical trial arena (233, 338). Various cell subtypes have been (magnetically) isolated on the basis of specific antibody binding, or pre-plating in fibronectincoated culture dishes (yielding cell aggregates known as cardiospheres), therefore producing c-kit⁺/lineage⁻ cells, Isl1 cells (193, 208, 436) and cardiosphere-derived c-Kit⁺/Sca-1⁺ cells. These cells are proposed as adult, multipotent stem cells, capable of self-renewal in culture,

and of differentiating into several cardiac lineages, such as endothelial cells, smooth muscle cells and cardiomyocytes.

CPCs/CSCs can participate to cardiac regeneration (193, 208, 237, 252, 436) and cardioprotection by releasing paracrine factors such as insulin growth factor (IGF), granulocyte-colony stimulating factor (G-CSF), VEGF, and stem cell-derived factor (SDF)-1 α (20, 260, 319, 363), although to date there is little data documenting the extent and burden of this process in the adults. CPCs/CSCs differentiation may be also responsible of the late-onset ANT-induced CTX, which is an important issue in pediatric oncology (147, 158). CPCs/CSCs may be sensitive to interference from a wide range of anti-cancer drugs, resulting in accumulation of oxidative DNA damage, growth arrest, inhibition of CPCs/CSCs proliferation, cell senescence, expression of p53, telomere attrition, and cell necrosis and apoptosis (67, 72). In particular, anti-cancer chemotherapy may inhibit the expression of c-kit, resulting in impairment of CPCs/CSCs mobilization in the damaged area (107), and may impair several signaling pathways including Akt, VEGF, and Notch (251).

Therefore, the idea that autologous CPCs/CSCs can be obtained before antineoplastic drug treatment and used in cancer patients sensitive to antineoplastic CTX, for management or prevention of HF, has been proposed (67, 289). Repopulating the damaged heart by boosting endogenous CPCs/CSCs may represent an alternative strategy by which these cells can contribute to myocardial protection, neovascularization, and the reduction of cardiac fibrosis after chemotherapy-induced CTX (76, 360). However, since the actual existence of CPCs/CSCs and their regenerative capacity have been questioned and are still controversial (with specific reference to the c-kit cells (375, 404-406), further studies are required to clarify several critical questions (e.g. the burden of endogenous cardiac regenerative process supported by CPCs/CSCs, identification of the molecular mechanisms by which protection, regeneration, and neovascularization may occur), before these approaches are introduced in clinical practice. Indeed, among stem cells, induced pluripotent stem cells (iPSCs) are of great interest for research and application in regenerative medicine, disease modeling, drug discovery and in the determination of drug toxicity (83). All these aspects need to be further investigated. Considering all these perspectives, animal studies which model risk factors for CVD and comorbidities are currently essential for adequate successive clinical translation. Basic and translational studies may help to identify novel and highly effective therapeutic strategies to prevent CTX induced by anticancer therapeutics. The main aim of these studies must be the early identification such cardiovascular alterations, thus preventing their CV side-effects, and the development of more personalized treatments. In this regard, the addition of genetic profiling to clinical risk factor assessment is expected to assist in identifying subjects at high risk of developing CTX in the future. There is an urgent need to close this gap in our knowledge in order to identify and establish optimal strategies of prevention and management that balance effectiveness of cancer therapy with long-term health (232, 425). This is a particularly delicate task, since redox signaling is involved in both mitogenic regulation and tumor suppression (156). Also, on one side, experimental data suggest that antioxidants may be effective in shielding the the cardiovascular system from toxicity, but on the other, clinical use of cardioprotective antioxidants is controversial because of the potential reduced cytotoxic efficacy against cancer. Further experimental and clinical studies, in particular well designed randomized clinical trials, are therefore needed to assess this important issue (412).

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List of Abbreviations

5-FU: 5-Fluorouracil

ACE-Is: Angiotensin-converting enzyme inhibitors

AMPK: AMP-activated protein kinase

ANTs: Anthracyclines

APCs: Antigen-presenting cells

ARBs: Angiotensin receptor blockers

ASK1: Apoptosis signal-regulating kinase 1

ATE: Arterial thromboembolic events

Bcl-2: B-cell leukemia/lymphoma

BDNF: Brain-derived neurotrophic factor

BNP: Brain natriuretic peptide

CML: Chronic myeloid leukemia

CMR: Cardiac magnetic resonance

CSCs: Cardiac stem cell cardiotoxicity

CSF1R: Colony-stimulating factor 1 receptor

CTLA-4: Cytotoxic T lymphocyte-associated protein 4

CTX: Cardiotoxicity

CV: Cardiovascular

CVD: Cardiovascular disease

ECG: Electrocardiogram

ERK: Extracellular signal-regulated kinase

FLT3: FMS-related tyrosine kinase 3

HF: Heart failure

IL-6: Interleukin 6

IRAEs: Immune-related adverse events

JNK: c-Jun N-terminal kinase

LV: Left ventricle

LVEF: Left ventricular ejection fraction

MAPK: Mitogen-activated protein kinase

mPTPs: Mitochondrial permeability transition pores

MUGA: Multiple-gated acquisition

NO: Nitric oxide

NOSs: Nitric oxide synthases

NOXs: NAD(P)H oxidases

NRG-1: Neuregulin 1

PAD: Peripheral arterial disease

PAH: Pulmonary arterial hypertension

PD-1: Programmed cell death protein 1

PDGFR: Platelet-derived growth factor receptor

PD-L1: Programmed death-ligand 1

PERK: PRKR-like endoplasmic reticulum kinase

RNS: Reactive nitrogen species

ROS: Reactive oxygen species

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Figure legends

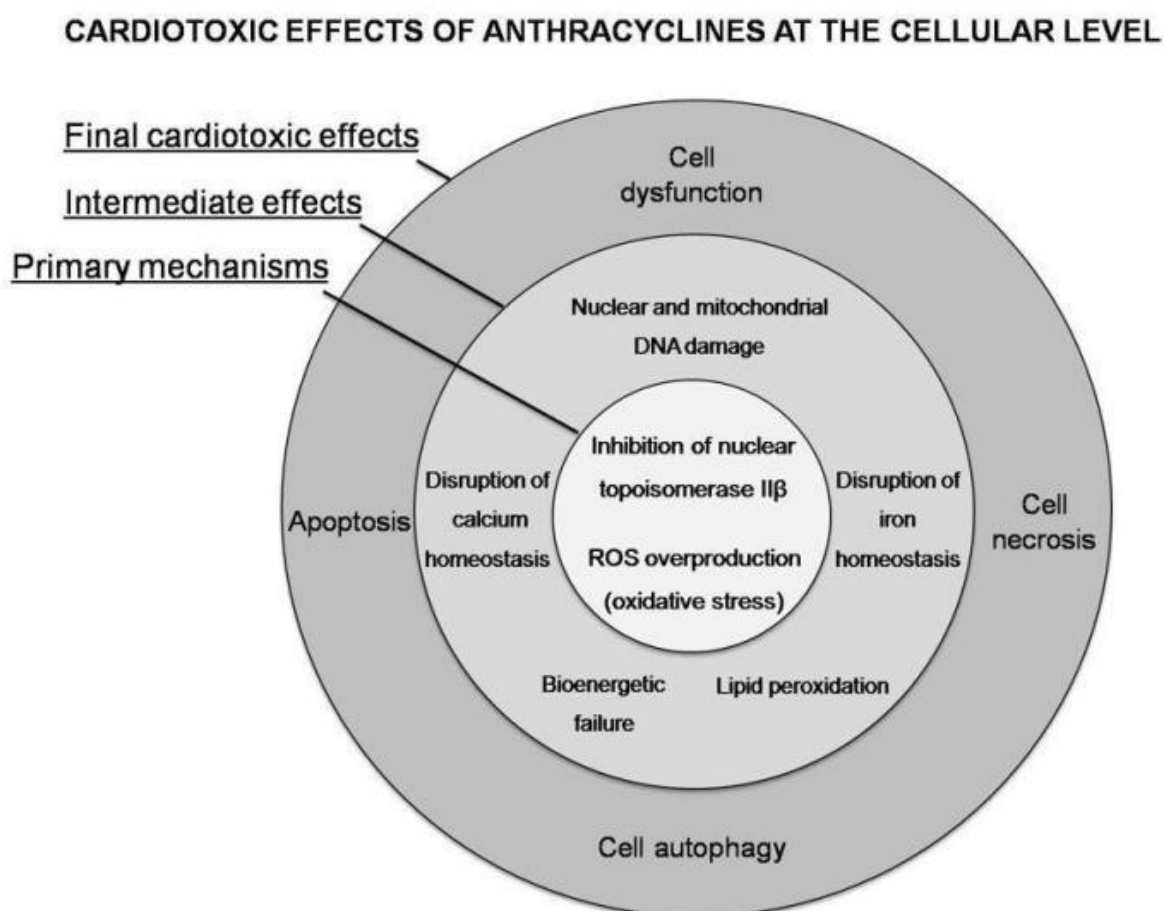


Figure 1. Concentric representation of cardiotoxic effects of anthracyclines.

PREDISPOSING FACTORS ACCOUNTING FOR INDIVIDUAL VARIABILITY OF ANTHRACYCLINE CARDIOTOXICITY

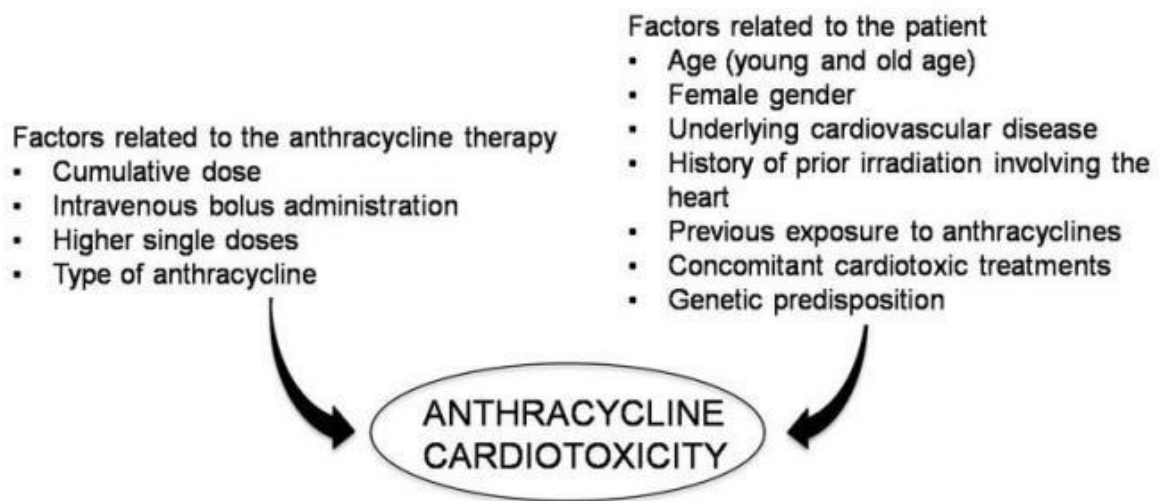


Figure 2. Simplified algorithm showing the factors related to anthracycline therapy or patient characteristics that may determine cardiac damage.

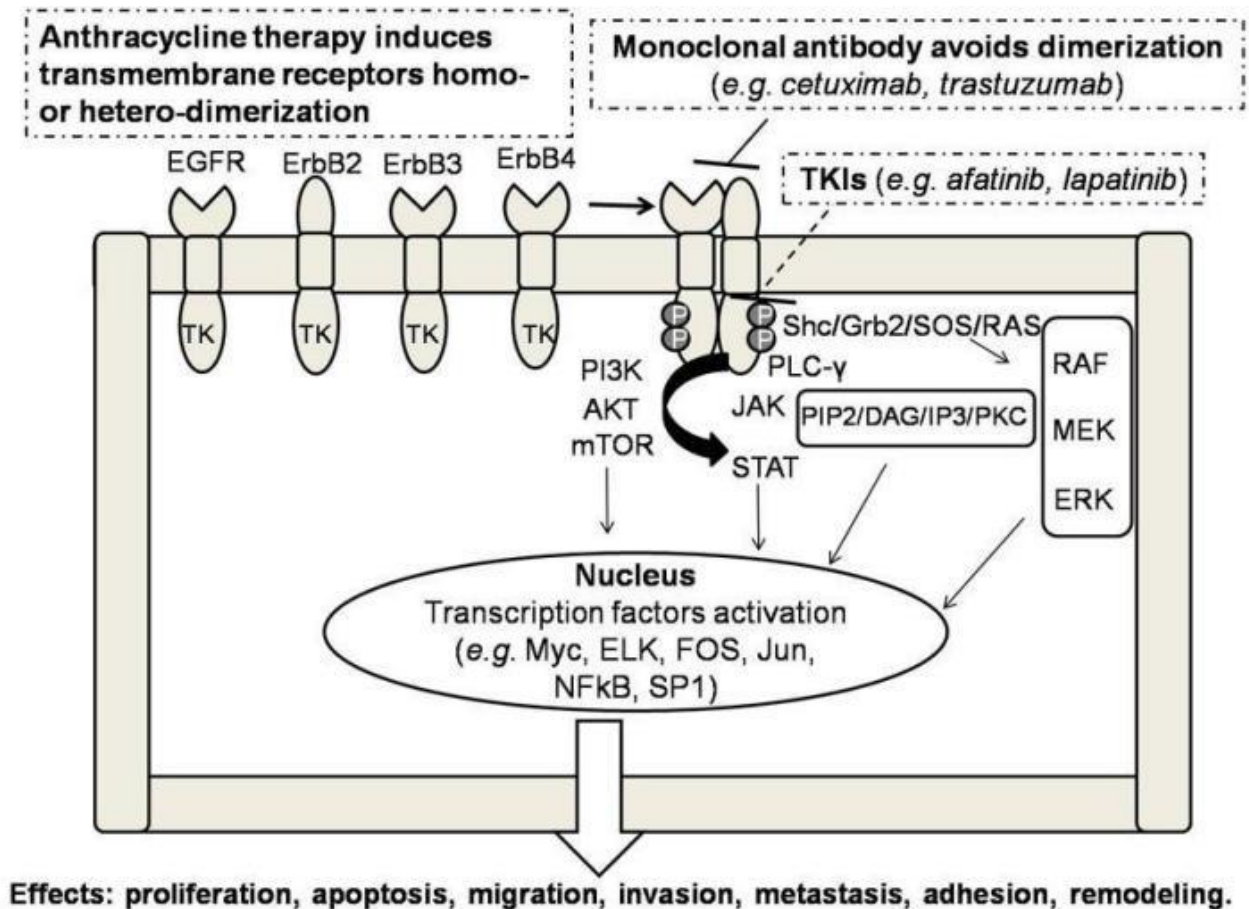


Figure 3. ErbB receptor homodimerization or heterodimerization is induced by stressors, including anthracycline therapy, with consequent complex intracellular pathway activation. Cascade effects can be avoided by treatment with monoclonal antibodies and tyrosine kinase inhibitors (TKIs). See the text for further explanation and acronyms.

Anti-angiogenic drugs disrupt the VEGF signaling cascade
(e.g. bevacizumab, sorafenib, sunitinib, pazopanib and vandetanib)

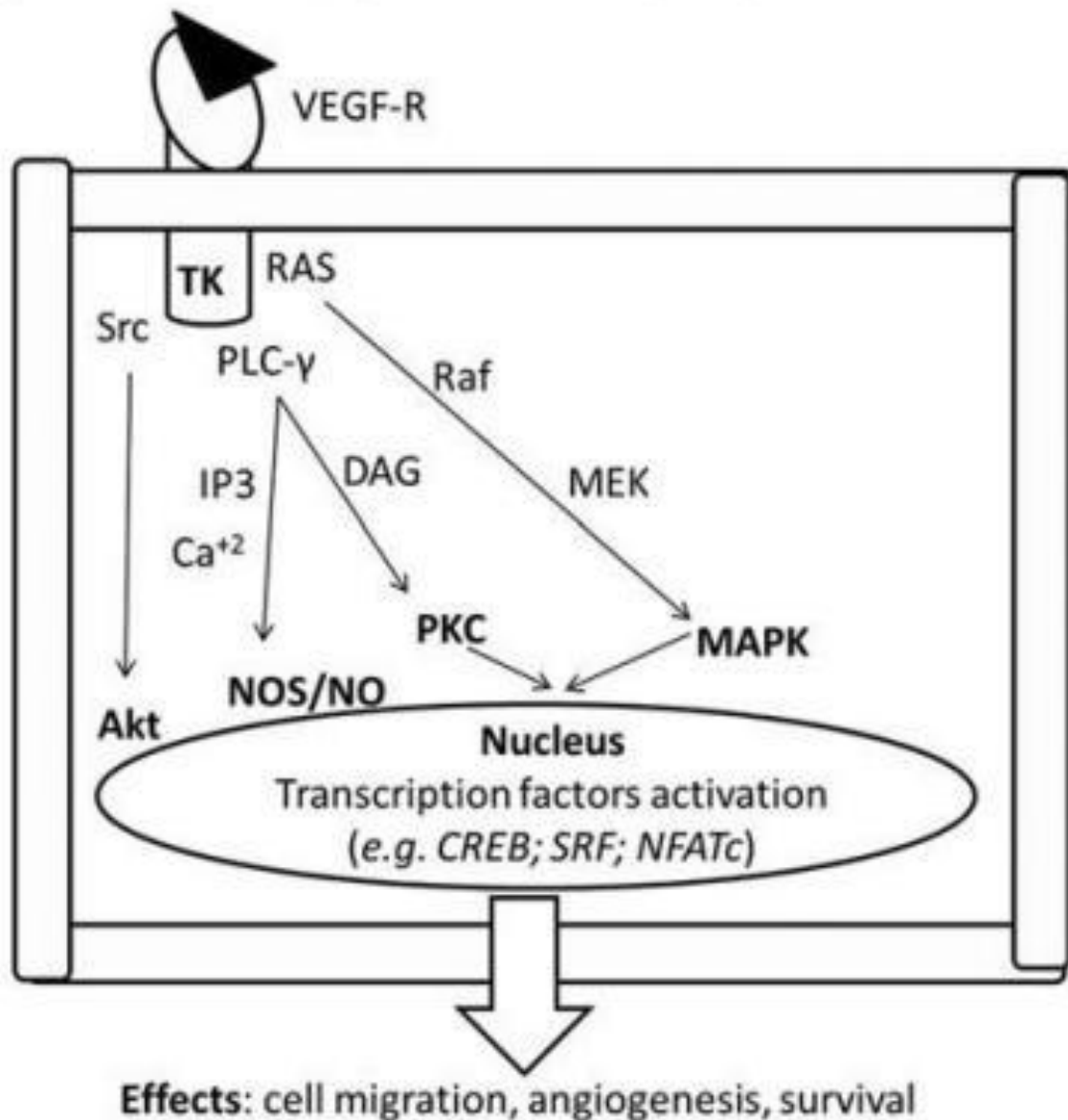


Figure 4. Vascular endothelial growth factor receptor (VEGFR) activation triggers a complex intracellular pathway. Cascade effects can be avoided by treatment with anti-angiogenic drugs acting at various levels of the cascade. See the text for further explanation and acronyms.

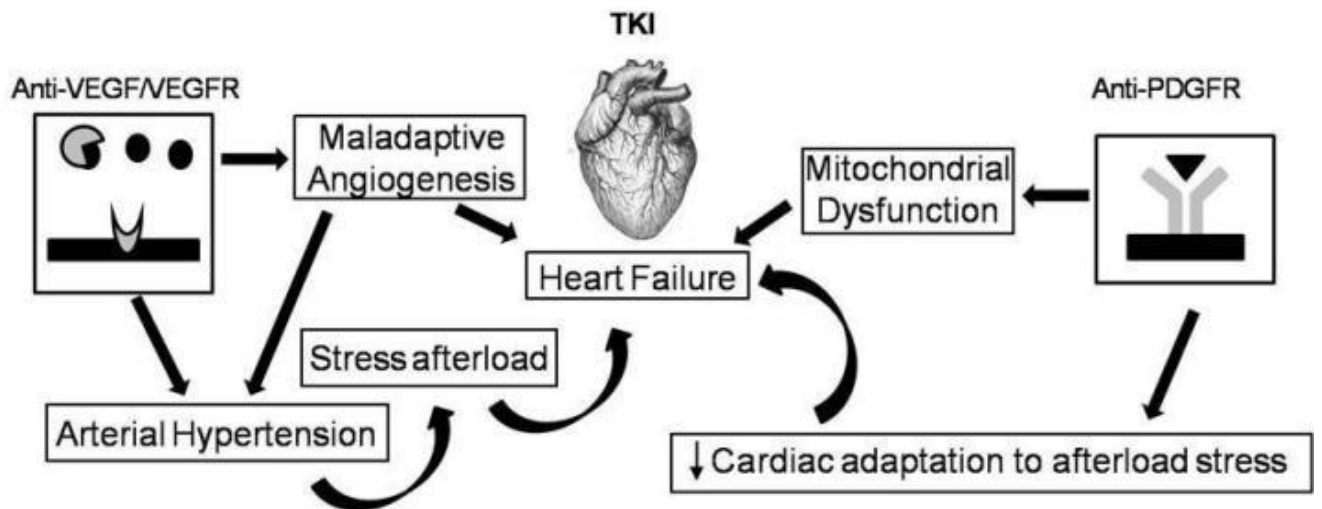


Figure 5. Schematic illustration of how tyrosine kinase inhibitor (TKI) antagonists induce cardiac damage; these drugs can increase arterial pressure and ventricular-vascular coupling, leading to heart failure.

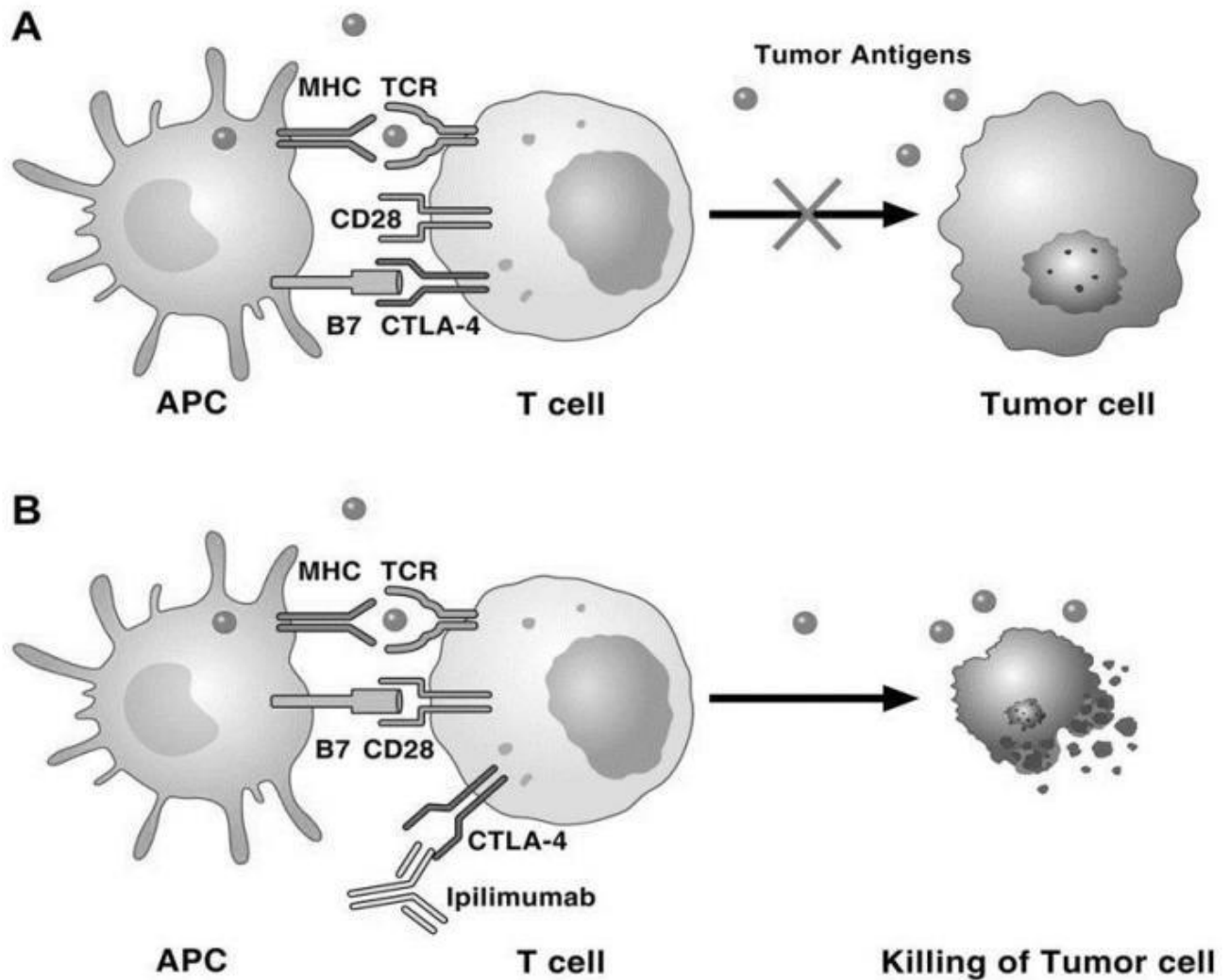


Figure 6. A) Dying tumor cells release tumor neo-antigens that are taken up by antigenpresenting cells (APCs), which then present B7 co-stimulatory molecules to T cells. T cells recognize tumor neo-antigens on APCs and are activated. Activated T cells upregulate inhibitory checkpoints, such as CTLA-4 and PD-1, which block T cell activation and attack of tumor cells. B) Ipilimumab blocks CTLA-4, resulting in T cell activation and destruction of tumor cells. See the text for further explanation and acronyms.

Mechanism of Antimetabolites Cardiotoxicity
(e.g. 5-FU, capecitabine and gemcitabine)

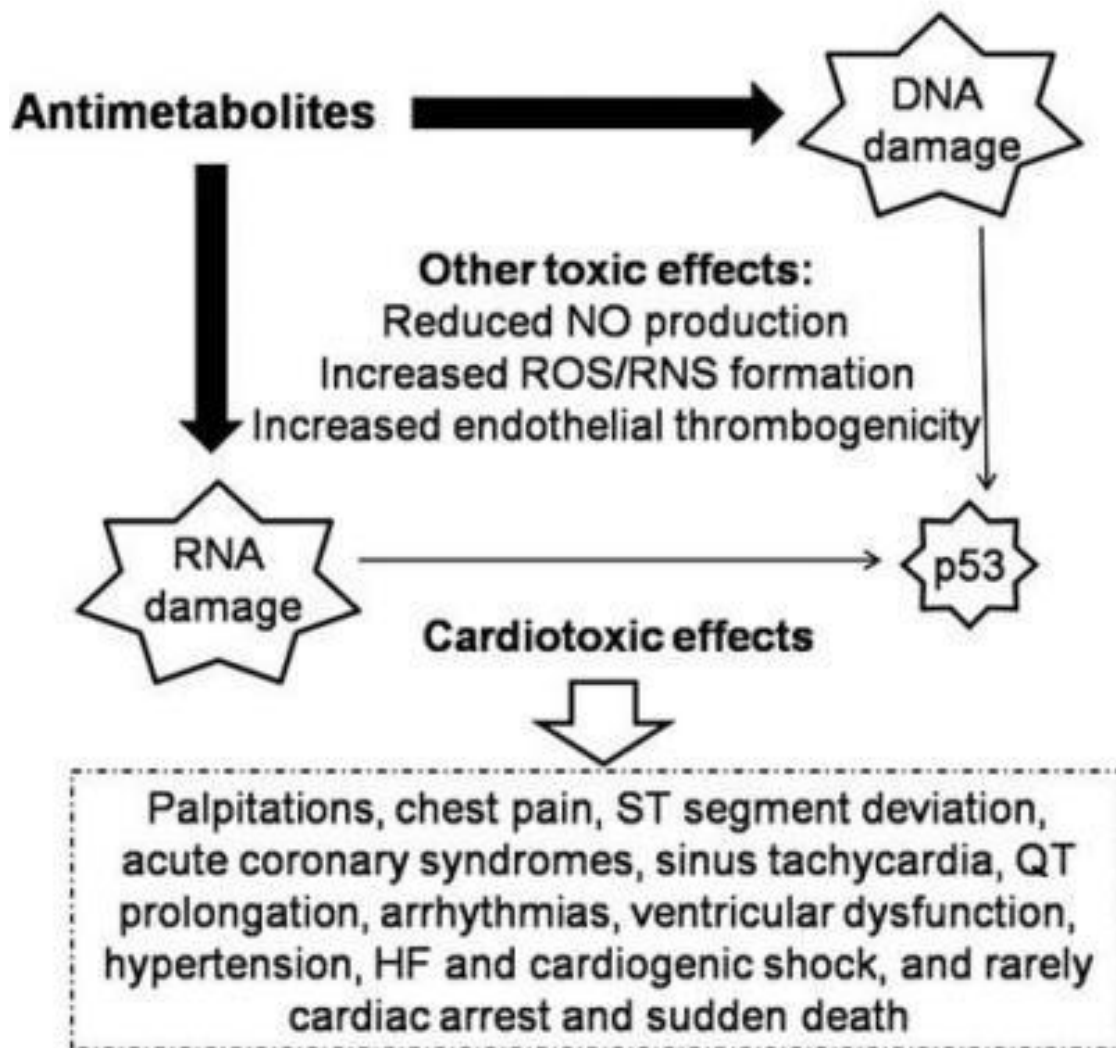


Figure 7. Main cardiotoxic mechanism and effects induced by antimetabolite drugs. See the text for further explanation and acronyms.

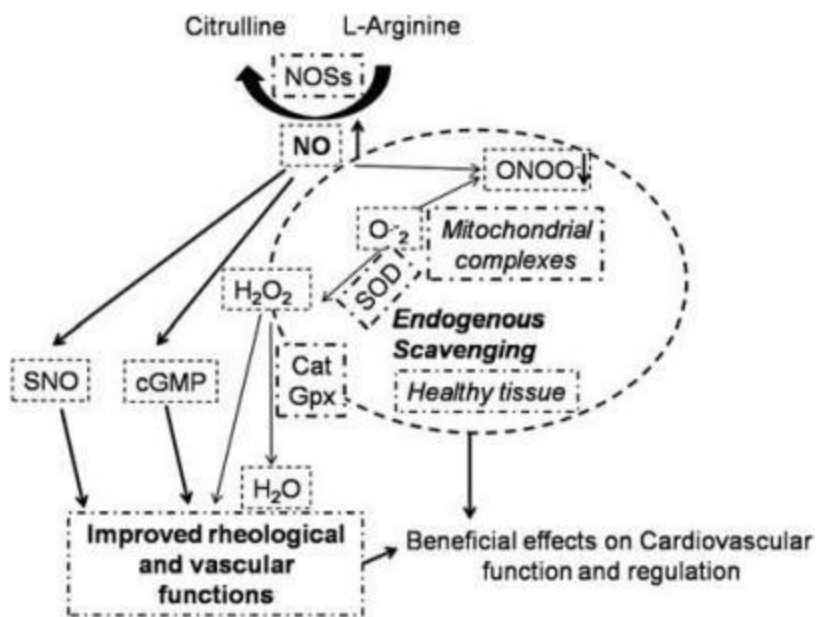


Figure 8. Physiological function of the redox system. See the text for further explanation and acronyms.

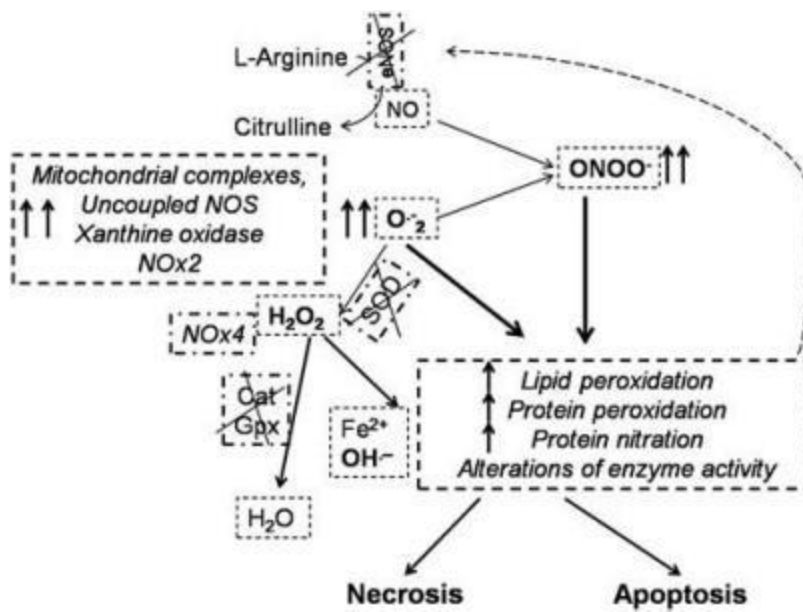


Figure 9. In the case of excessive production of superoxide anion (O_2^-) and other reactive oxygen species (ROS)/reactive nitrogen species (RNS), lipid and protein oxidation/nitration may occur, with consequent alteration of the activity of many enzymes, leading to cell death. The dashed arrow represents the onset of a vicious cycle affecting redox enzymes. See the text for further explanation and acronyms.

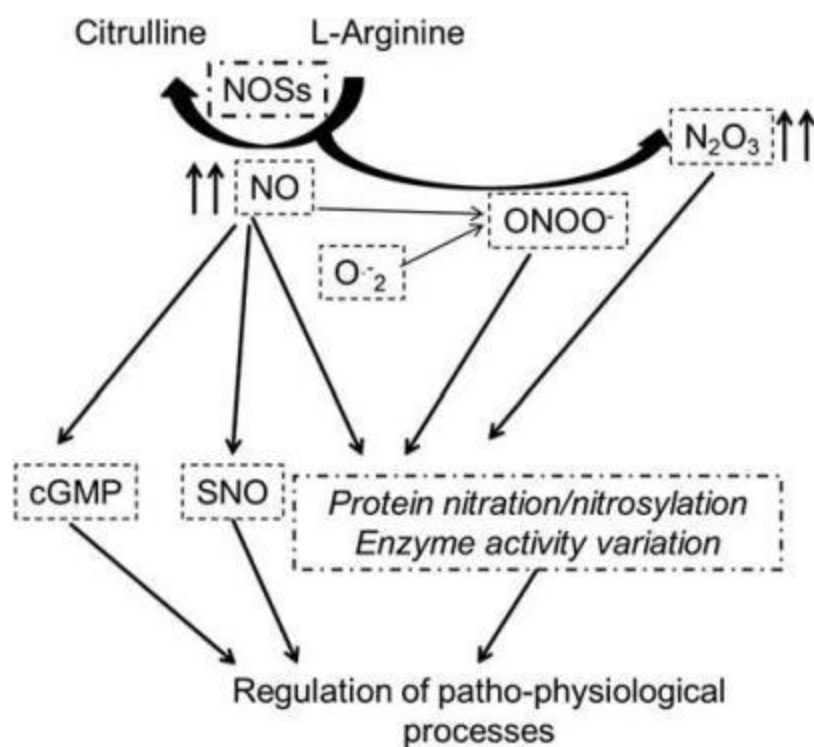


Figure 10. Antioxidant properties of nitric oxide (NO). When production of NO is adequate, the formation of nitrosylating agents may prevail, including N_2O_3 , which can mediate a direct thiol nitrosylation of proteins, which in turn may affect the regulatory function in many physiological processes. See the text for further explanation and acronyms.

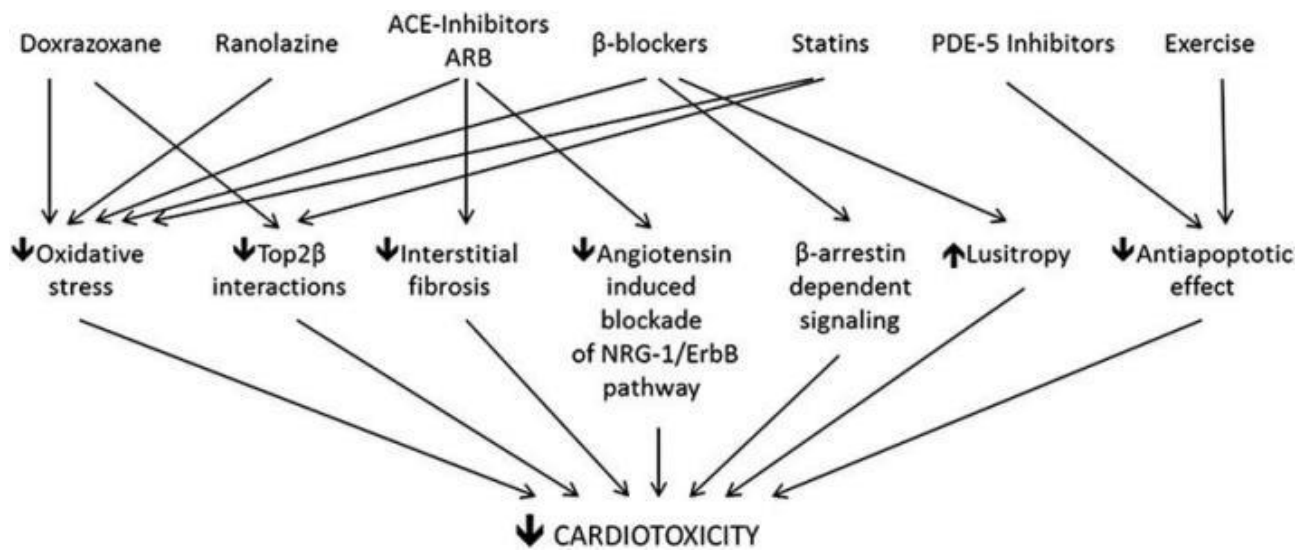


Figure 11. Drugs and cardioprotective strategies against antineoplastic-induced cardiotoxicity. The main mechanism(s) of protection are reported. See the text for further explanation and acronyms.

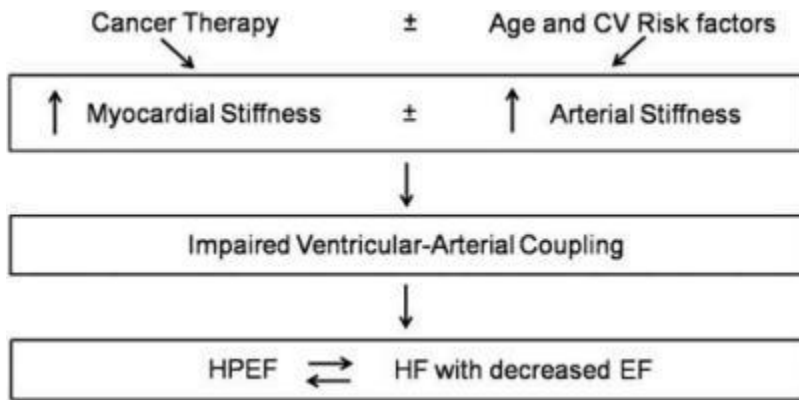


Figure 12. Simplified algorithm showing how cancer therapy alone or together with demographic and conventional risk factors may determine cardiac damage; both factors can increase myocardial and arterial stiffness, thus impairing ventricular-vascular coupling and finally leading to heart failure (HF), either with decreased ejection fraction (EF) or preserved EF (HFPEF).

TABLE 1. DRUGS: INDICATIONS AND ASSOCIATED TYPES OF CARDIOVASCULAR TOXICITY

Class/drug	Indication	Toxicity
Anthracyclines Doxorubicin, daunorubicin, epirubicin	Breast cancer, leukemia, lymphoma, ovarian cancer, sarcoma	LV dysfunction/heart failure (2-48% incidence)
Anti-ErbB2 Trastuzumab, lapatinib, pertuzumab	Breast cancer, gastric cancer	LV dysfunction (0.2-20.1% incidence)
Vascular endothelial growth factor (VEGF) inhibitors and multi-targeted kinase inhibitors Bevacizumab, sunitinib, sorafenib, regorafenib, pazopanib, axitinib, vandetanib	Gastrointestinal cancer, hepatocellular carcinoma, renal cell carcinoma,	LV dysfunction (2.7-19% incidence), Hypertension (15-44% incidence), Vascular damage (1.4-3.8% incidence)
Tyrosine kinase inhibitors (TKIs) and anti-BCR-abl agents Imatinib, nilotinib, dasatinib, bosutinib, ponatinib	Chronic myeloid leukemia	Edema, cardiac dysfunction (0.2-4% incidence), QTc prolongation (2-40.5% incidence)
Taxanes docetaxel, paclitaxel	Breast cancer, colorectal cancer, non-small cell lung and ovarian cancers	Bradycardia, LV dysfunction, ischemia (0.3-1.7% incidence)
Cancer Immunotherapies Ipilimumab, nivolumab, pembrolizumab, atezolizumab	Metastatic melanoma Metastatic non-small-cell lung cancer (NSCLC) Advanced Renal cell carcinoma Classical Hodgkin lymphoma Advanced urothelial carcinoma	Immune myocarditis (0.01-0.27% incidence)
Antimetabolites Fluorouracil (5-FU), capecitabine, gemcitabine	Gastrointestinal, breast, head, neck, and pancreatic cancer	Coronary spasms/ischemia (7-18% incidence)
Proteasome inhibitors bortezomib; carfilzomib, ixazomib, delanzomib, oprozomib, and marizomib	Multiple myeloma and other hematologic conditions (amyloidosis, non-Hodgkin lymphoma)	LV dysfunction (2-25% incidence)

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TABLE 2. DRUGS PROTECTIVE AGAINST ANTHRACYCLINE CARDIOTOXICITY

<i>Treatment</i>	<i>Mechanism</i>	<i>Results</i>
Dexrazoxane	ROS reduction	HF↓
	Reduction in DNA damage	
Statins	Reduction in DNA damage	HF↓
	Reduction in cardiac fibrosis	
ACE inhibitors	ROS reduction	HF↓
	Reduction in cardiac fibrosis	
	Downregulation of NRG-1/ErbB pathway	
β blockers	Downregulation of catecholamine stimulation	HF↓
	Enhanced lusitropy	

HF heart failure, *ACE* angiotensin-converting enzyme, *ROS* reactive oxygen species

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TABLE 3. PREVENTION STRATEGIES FOR CARDIAC DYSFUNCTION INDUCED BY THE MAIN CLASSES OF ANTINEOPLASTIC DRUGS

<i>Drugs</i>	<i>Prevention strategy</i>	<i>Rationale/Mechanisms of action</i>
Anthracyclines	Lowering of lifetime cumulative doses	Dose-dependent cardiotoxicity
	Usage of epirubicin, less cardiotoxic than doxorubicin	
	Avoiding bolus, preferring infusional schedules	
	Liposomal formulations	Lowering oxidative stress, preventing the interactions between anthracyclines and Top2 β
	Dexrazoxane	
	ACE-1, ARBs	Lowering oxidative stress, reducing interstitial fibrosis, enhancing intracellular calcium handling, cardiomyocyte metabolism and mitochondrial function
	β blockers	Preserving EGF signaling via a β -arrestin-dependent mechanism, lowering oxidative stress, improving lusitropy
HMG-CoA reductase inhibitors	HMG-CoA reductase inhibitors	Inhibiting Top2 β -mediated DNA damage, antioxidant and anti-inflammatory effects
	Ranolazine	Lowering oxidative stress
	PDE-5 inhibitors	Anti-apoptotic effects
	Physical exercise	Lowering oxidative stress and pro-apoptotic signaling, enhancing calcium handling, enhancing myocardial energetics
Anti-ErbB2	ACE-1, ARBs	Decrease in angiotensin-induced blockade of NRG-1/ErbB pathway
	β -blockers	Stimulating β -arrestin-dependent signaling, with subsequent activation of ErbB2-mediated cardioprotective pathways
	Anti-angiogenic drugs (sorafenib and sunitinib)	Counteracting hypertension-dependent damage
Metformin	Metformin	Enhancing myocardial energetics via activation of cAMP-kinase

ARBs angiotensin II receptor blockers, EGF epidermal growth factor, HMG-CoA hydroxymethylglutaryl-coenzyme A, PDE-5 phosphodiesterase-5, NRG-1 neuregulin 1, ErbB epidermal growth factor receptor, cAMP cyclic adenosine monophosphate Modified from 33

TABLE 4. ASSESSEMENT OF ANTI-CANCER CARDIOTOXICITY

<i>TECHNIQUE</i>	<i>DIAGNOSTIC CRITERIA</i>	<i>ADVANTAGES</i>	<i>DISADVANTAGES</i>
Echocardiography	LVEF: >10% decrease with a value	Availability	Reproducibility
1. LVEF	<50% identify patients with	Safety	Image quality
2. GLS	cardiotoxicity	Comprehensive cardiac	GLS: Intervendor
	GLS: >15% relative percentage	assessment	variability; low specificity
	reduction from baseline may	Ideal for serial evaluations	
	identifies patients at risk for	Low cost	
	cardiotoxicity	GLS: Sensitivity (early CTX)	
Nuclear cardiac imaging (MUGA)	>10% decrease in LVEF with a value <50% identifies patients with cardiotoxicity	Reproducibility	Cumulative radiation exposure No information on other cardiac structures and pericardium Not recommended for serial examinations
Cardiac magnetic resonance (CMR)	Useful if other techniques are non-diagnostic or to confirm the presence of LV dysfunction in borderline LVEF value	Accuracy, reproducibility RV and pericardium assessment Detection of edema, inflammation, and fibrosis (early and late CTX) Arterial stiffness measurement	Limited availability Patient adaptation General contraindications High cost Low feasibility for serial examinations
Cardiac biomarkers: - Troponin I	Any increase identifies pts who may benefit from ACE-Is	Accuracy, reproducibility Wide availability	Poor evidence for subtle rises
- Hs Troponin I	New elevation of Hs-Troponin I	High sensitivity	Variability with different assays
- BNP*	predicts LV dysfunction		Unclear role for routine surveillance
- NT-proBNP*			

pts = patients; *more useful for their negative predictive values

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TABLE 5. CARDIAC BIOMARKERS TO DETECT CARDIAC TOXICITY

Cardiac Biomarkers	Typical Mechanisms of Release	Anti Cancer Drugs
Troponins (troponin I and T)	Ischemia, inflammation and oxidative stress	Anthracyclines; Anthracycline-adjuvant trastuzumab.
Natriuretic peptides (BNP pro-BNP)	Increase in myocardial wall stress and left ventricular filling pressure	Anthracyclines; Various high-dose chemotherapy protocols.
Fatty acid binding protein (FABP) Glycogen phosphorylase BB (GPBB)	Ischemia and necrosis	Anthracyclines
Circulating microRNAs (miR-146a)	Altered homeostasis	Anthracyclines (pre-clinical studies)